pheasants, goldeneye, and black-headed gulls. While the 1,000 µg/kg dosage of TCB resulted in complete embryolethality, the dose-response relationship for this toxicity must be rather steep, as a 100 µg/kg dosage had no effect on hatchability. Likewise the dosages of TCB injected into the eggs of the other bird species had no affect on the hatchability of these eggs. As these dosages resulted in a final TCB concentration in the embryos of chicken, pheasant, and goldeneye of 0.18, 1.0, and 1.10 ppm, respectively, the species differences observed in embryolethality of the above birds species are not related to differences in the TCB concentrations actually achieved in the embryos.

3.4.6 Summary of Reproductive Toxicity

Studies of the reproductive toxicity of PCB mixtures and congeners in mice, rats, mink, ferrets, monkeys, and other species suggest that there is considerable interspecies variation in sensitivity to the reproductive effects of these compounds.

Mice appear to be the least sensitive species tested. While mice fed Aroclor 1254 were shown to have decreased conception rates and decreased survival of offspring at postnatal day 28, these effects were generally associated with Aroclor 1254 levels of 100 ppm in the feed. Other studies in mice have demonstrated that PCBs cross the placenta and are transferred to the yolk sac, amniotic fluid, and fetus. Investigations of PCB transfer from the mother to offspring via nursing suggest that mother's milk provides greater PCB exposure than that which occurs *in utero*. If the PCB exposure from breastmilk is sufficiently high, PCBs may decrease neonatal survival.

Reproductive studies in rats suggest the threshold for reproductive toxicity occurs at dietary levels of approximately 100 ppm for commercial mixtures of 54% chlorine content. The threshold for 60% chlorine content mixtures appears to be greater than 100 ppm. As with mice, studies in rats indicate that neonatal exposure to PCBs via milk is greater than is transplacental exposure to the fetus. Thus, decreases in pup survival appear to result from acute toxicity prior to weaning rather than some developmental defect that limits pup survival. While Aroclor 1254 (10 mg/kg/day) administered to female rats has also been reported to

prolong the estrous cycle, decrease sexual receptivity, cause vaginal bleeding during gestation, delay parturition, and decrease litter size, chronic studies indicate this dosage would result in mortality if the exposure duration were extended.

Mink reproductive success is adversely affected by PCB at lower levels than most species. Reproductive studies in mink indicate that more highly chlorinated are considerably more toxic than less-chlorinated PCB mixtures. For example, Aroclors 1242, 1221, and 1016 do not appear to cause significant reproductive effects following chronic exposure to dietary levels of 2 ppm or less, while a 1 ppm dietary level of Aroclor 1254 is safe only if the exposure is for six months or less. It is important to note that the dietary levels of PCBs causing reproductive failure in mink are very close to those producing mortality. Given this observation and the fact that neonates receive a large percentage of their mother's PCBs via milk, mink reproductive problems appear to occur secondary to severe systemic toxicity.

Studies in monkeys, although limited by small experimental groups, suggest that PCB-treated mothers may have smaller infants, that gain weight less rapidly and have areas of hyperpigmented skin. Infants born to and nursed by PCB-treated mothers developed acne and facial edema within two months after birth. Three of six infants born to monkeys treated with 2.5 ppm PCB in the diet died within eight months after birth. Thymic atrophy, small spleens, thickening of the gastric mucosa, and liver effects were observed in some of these monkeys at autopsy. It is believed that PCB intake during nursing was primarily responsible for the toxic effects observed in these infants.

The reproductive toxicity of PCBs has been studied to a limited extent in other species, e.g. rabbits, but few additional toxicities or new findings have resulted from these efforts. One exception is the fact that birds may excrete substantial quantities of PCBs in the eggs they lay. If sufficient concentrations are transferred to the egg, embryolethality may occur. As with other toxicities, however, there are considerable species/strain variations among birds regarding the dietary level of PCBs necessary to result in reproductive failure.

3.5 TERATOGENICITY

3.5.1 Morphological Studies in Mice

The studies concerned with the teratogenicity of PCBs in mice are contradictory. Toeruek (1973) has reported that a 500 mg/kg dose of PCBs was not teratogenic in mice when given on days 1-6 or 7-11 of gestation. Similarly, a number of reproductive toxicity studies of PCBs (studies designed to evaluate reproduction but continued PCB administration through gestation) have shown PCBs to be without teratogenic effects (Torok, 1976; Mattsson et al., 1981; Orberg, 1978; Vodicnik et al., 1980). The fact that no terata were reported in these studies suggests that at least no gross physical defects were caused by PCB administration. More recently, however, other studies have reported that PCBs are capable of inducing teratogenic effects in mice at doses which are considerably lower than the 500 mg/kg NOEL reported by Toeruek (1973).

Watanabe and Sugahara (1981) administered ten daily doses of one to five mg Kanechlor 500 by subcutaneous injection into the backs of pregnant ddY strain mice on days 6 through 15 of gestation. The weight of the animals ranged from 26-29 g, and after all ten doses were given, the total amount of PCBs administered to each mouse ranged from 10-50 mg of PCBs. The corresponding daily dosage range derived from these numbers is therefore 34.5-192.3 mg/kg/day, and the total experimental dosage would be about 345-1,923 mg/kg. The authors reported finding an increased incidence of cleft palate in the offspring born to mothers dosed with Kanechlor 500. However, the following statement made by the authors is clearly not supported by the data:

> *There was no significant differences among the various groups in maternal weight gain or fetal body weight, although some dams injected with PCB showed skin lesion, alopecia, or swelling of the liver. These results suggest that the PCB used in these experiments has a specific teratogenic effect, and the results are not due to general maternal toxicity.*

As can be seen in Table 3.5.1, as the total dose is increased from 10-100 mg the pregnancy rate decreases in a dose-related manner to 19%, a value one-fifth that of

the control animals. More importantly, the maternal mortality increases from 0% to 27%, a change most toxicologists would consider representative of a significant increase in maternal toxicity. In fact, it is clear from the data in Table 3.5.1 that maternal toxicity (lethality) is an effect with a lower threshold and steeper dose-response curve than the teratogenic effect being investigated, i.e. the percent increase in maternal lethality is 1.5-2.0 times the incidence of cleft palates at the three highest doses. The total dose given to the high-dose group is about 2,000 mg/kg, a dose which approximates the LD_{50} for rodents when mortality is measured over a period of a few weeks instead of the more common 24-hour observation period normally used to measure acute toxicity. Thus, it is not surprising that Watanabe and Sugahara (1981) observed maternal mortality in the higher dose groups. Therefore, this study merely serves to demonstrate that while Kanechlor 500 might be considered a weak teratogen, this effect is only observed at maternally toxic and lethal doses. However, teratogenicity is not a particularly unusual nor unexpected finding when one examines the reproductive effects of a chemical at high and systemically-toxic doses.

Marks et al. (1981) examined the teratogenic effects of the PCB isomer 3,3',4,4',5,5'-hexachlorobiphenyl when given by gavage at doses of 0.1, 1, 2, 4, 8, and 16 mg/kg/day on days 6-15 of gestation. On day 18 of gestation all of the dams were killed and their fetuses examined for external, visceral, and skeletal abnormalities (see Table 3.5.2). Besides the reported teratogenic effects, the other adverse effects observed in this study included:

- a decrease in the weight gain of the dam was evident at the two highest doses tested but was only significant at the 8 mg/kg/day dose,
- the number of resorbed fetuses was significantly increased at the 8 and 16 mg/kg/day doses,
- there was a significant decrease in the average number of live fetuses per dam at doses of 4 mg/kg/day or higher,
- the average fetal weight was lower than normal at the 8 mg/kg dosage only, and
- at doses of 2 mg/kg/day and above there was a significant increase in the percentage of malformed fetuses, an effect which reached an incidence of 60% at the two highest doses tested.

Table 3.5.1

Cleft Palate Induced by PCB in Mice

Total dose (in mg's per dam)	Dam with fetal cleft palate	Fetal cleft palate	Resorbed and dead fetus	Pregnancy rate	Mortality of dam
100	2/3 (67%)	5/28 (18%)	6/34 (18%)	3/16 (19%)	6/22 (27%)
50	7/24 (29%)	13/225 (6%)	24/249 (10%)	24/78 (31%)	11/89 (12%)
40	6/32 (19%)	12/307 (4%)	34/341 (10%)	32/49 (65%)	3/52 (6%)
30	6/26 (23%)	9/253 (4%)	27/280 (10%)	26/44 (59%)	1/45 (2%)
20	4/44 (9%)	4/418 (1%)	28/446 (6%)	44/50 (88.0)	0/50 (0%)
10	1/51(2%)	1/514 (<1%)	37/551 (7%)	51/65 (79%)	0/65 (0%)
0	0/65 (0%)	0/631 (0%)	35/666 (5%)	65/69 (94%)	1/70 (1%)
No treatment	0/112 (0%)	0/1134 (0%)	63/1197 (5%)	112/119 (94%)	0/119 (0%)

* Percentage of the incidence for each effect is given in parentheses.
Adapted from Watanabe and Sugahara (1981)

As in the previous study, the authors stated that the embryotoxic and teratogenic effects of the hexachlorobiphenyl occurred independent of maternal toxicity. However, the only evidence of maternal toxicity apparently acknowledged by these authors was a greater than 10% decrease in the mean weight gain of the dams, clear signs of overt toxicity, or maternal mortality. None of these measures of maternal toxicity is particularly sensitive. Contradicting their conclusion that maternal toxicity had not occurred in this study were the histopathologic changes they reported observing in the livers of PCB-treated dams. The changes noted were:

> *Maternal liver changes included moderate to marked swelling of hepatocytes, single cell necrosis, primarily around the central veins, and occasional microabscesses. In contrast, fetal liver changes included massive necrosis in the hepatic lobules and the formation of a tubule-like pattern of hepatocytes.*

Thus, although the authors had actually observed substantial systemic toxicity in the form of liver injury, they apparently did not consider these changes to be evidence of maternal toxicity. The authors also cite unpublished work from their laboratory indicating that both 3,3',4,4'-tetrachlorobiphenyl and 2,2',3,3',4,4'-hexachlorobiphenyl were also teratogenic, but at higher doses than those used in this study. Without the actual data to evaluate, it is impossible to tell whether or not these responses only occurred at maternally toxic doses as well. This study, like that of Watanabe and Sugahara (1981), has little if any human relevance. The doses tested were excessive given the limited amount of this congener found in commercial mixtures. For this reason, and because the doses tested were obviously causing systemic toxicity to the dam, it cannot be concluded from this study that these PCB congeners respresent a significant reproductive hazard.

Mattsson et al. (1981) reported that doses of approximately 20-25 mg/kg/day of 2,2',4,4',5,5'-hexachlorobiphenyl did not increase resorption frequency, and no fetal changes were noted other than an enlargement of the liver caused by the inductive effects of PCBs. This is somewhat in contrast to the conclusion of the previous study by Marks et al. (1981) in which it was proposed that chlorination of the *meta*- and *para*- positions of the biphenyl ring leads to teratogenic effects.

Birnbaum et al. (1985) have reported that teratogenic interactions occur between 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and two hexachlorobiphenyl isomers (HCBs). In this study the administration of TCDD by gavage, at dosages of

Table 3.5.2

Mouse Fetal Anomalies Induced by 3,3',4,4',5,5'-Hexachlorobiphenyl

Malformations	Dosage (mg/kg/day)						
	0	0.1	1	2	4	8	16
External							
Cleft palate	2	4	5	20*	69*	118*	82*
Edema	0	0	0	0	1	0	0
Exenchephaly	2	2	0	0	0	0	0
Gastroschisis	1	0	0	0	0	0	0
Kinked tail	0	0	0	0	0	0	1
Open eye	2	2	0	0	0	0	0
Umbilical hernia	0	0	1	2	1	0	1
Total	7	8	6	22*	71*	118*	84*
Visceral							
Truncus arteriosus	1	0	0	0	0	0	0
Convoluted retina	0	0	0	0	0	0	1
Hydronephrosis	2	0	1	6	25*	83*	30*
Missing adrenal	0	0	0	0	2	0	0
Missing kidney	0	0	0	0	0	1	0
Total	3	0	1	6	27*	84*	31*
Discolored livers	1	0	7*	21*	38*	46*	24*
Undersized papilla	0	0	6	10*	27*	9*	0

* $p < 0.05$
Adapted from Marks et al. (1981)

12 μg/kg on gestational day 11, increased the incidence of fetal mortality and of fetal cleft palates in C57BL/6N mice. In fact, the latter effect increased from 0% to 36%. While dosages of 40 or 80 mg/kg 2,3,4,5,3',4'-HCB produced no fetal mortality or cleft palate, when these dosages were co-administered with TCDD the incidence of cleft palates rose to 60% and 65%, respectively. If the TCDD dosage was reduced to 3 μg/kg/day and administered on days 10-13 of gestation, the incidence of cleft palates induced by TCDD was minimal (4%); when TCDD was co-administered with 10 and 20 mg/kg of 2,3,4,5,3',4'-HCB, the incidence of cleft palates produced by TCDD increased to 20% and 42%, respectively.

In contrast to the enhancement caused by the 2,3,4,5,3',4'-HCB isomer, the co-administration of 2,4,5,2',4',5'-HCB with TCDD on days 10-13 of gestation had no effect on the incidence of cleft palates. A somewhat contradictory finding was the fact that even though the 2,3,4,5,3',4'-HCB isomer produced mild renal lesions when administered alone, neither HCB isomer enhanced the severity of TCDD-induced renal defects. The fact that the 2,3,4,5,3',4'-HCB isomer does not increase both of the TCDD-induced terata (cleft palate and renal defects) suggests that the potential for PCBs to enhance an adverse effect of TCDD must be tested on an organ-by-organ basis.

The question regarding whether or not the enhanced potency of TCDD caused by the 2,3,4,5,3',4'-HCB isomer should be considered a potentiation or synergistic effect was left undecided by the authors. Their indecision apparently rested on the fact that this isomer produced renal defects at the doses tested but did not produce cleft palate defects at these doses. Concerning the mechanism of the chemical interaction observed in this study, it may be postulated to be the result of : 1) receptor interactions at the *Ah* receptor, 2) a PCB-TCDD interaction at a second and more recently postulated receptor, or 3) another mechanism, e.g. the result of an altered tissue distribution of the TCDD molecule. Which, if any, of these th: possibilities is the explanation remains to be determined. These data do suggest, however, that large doses of specific PCB isomers may enhance some of the teratogenic effects of TCDD.

In contrast to the positive interaction reported by Birnbaum et al. (1985), Haake et al. (1987) have more recently found that a commercial PCB mixture such as Aroclor 1254 actually antagonizes the teratogenic effects of 2,3,7,8-TCDD. The administration of 20 μg/kg of 2,3,7,8-TCDD to pregnant C57BL/6J mice on day 10 of gestation resulted in a 62% incidence of cleft palates per litter without any observable evidence of maternal toxicity. In contrast, the administration of Aroclor 1254 at a dosage of 750 μmol/kg (i.e. 244 mg/kg) was not teratogenic, and when this dosage was co-administered with a 20 μg/kg dose of TCDD the incidence of cleft palates was diminished to only 8.2% per litter. Additionally, the number of litters with cleft palates reached 100% with 2,3,7,8-TCDD administration, while Aroclor 1254 co-administration decreased this number to only 35% (see Table 3.5.3). Thus, it appears that the most likely interaction to occur between dioxin and

Table 3.5.3

Interactions Between Aroclor 1254 and 2,3,7,8-TCDD

Treatment group	# of litters	liver/body weight(x100)	# litters with cleft palates	Fetuses with cleft palates (%)
Untreated	11	5.60 ± 0.42	1	1.3 ± 4.3
Corn oil (10 ml/kg)	11	5.74 ± 0.33	0	0.0 ± 0.0
2,3,7,8-TCDD (20 μg/kg)	10	6.38 ± 0.67*	10	61.8 ± 23.1*
Aroclor 1254 (244 mg/kg)	11	7.41 ± 0.56*	0	0.0 ± 0.0
Aroclor 1254 + 2,3,7,8-TCDD	17	9.25 ± 0.93*	6	8.2 ± 1.5**

* significantly different from the corn oil control, $p < 0.05$
** significantly different from TCDD group, $p < 0.05$

Adapted from Haake et al. (1987)

PCBs following an environmental exposure to these two chemicals is that the PCB mixture will probably antagonize the teratogenic potential of 2,3,7,8-TCDD as well as other TCDD-induced effects (Haake et al., 1987). This conclusion is also proposed by the authors of this paper who note that the ratio of PCB:TCDD used in this study is comparable to the ratio of these two chemicals typically found in the environment. Therefore, they suggest that low-level, nontoxic environmental PCB levels may actually afford some measure of protection against polychlorinated dibenzodioxins and polychlorinated dibenzofurans.

3.5.2 Neurobehavioral Studies in Mice and Rats

A series of studies have been reported demonstrating that when 32 mg/kg/day doses of 3,3',4,4'-tetrachlorobiphenyl (TCB) are given on days 10-16 of gestation (this is twice the dosage used by Marks et al. (1981) to produce cleft

palates in mice), this TCB isomer is capable of inducing a neurobehavioral syndrome in CD-1 mice (Tilson et al., 1979; Chou et al., 1979; Agrawal et al., 1981). The most severely affected mice were termed "spinners" because of their stereotypic circling behavior, head bobbing and hyperactivity (Tilson et al., 1979). Gross observations of the "spinners" revealed they suffered alopecia about the head and neck region, and that one eye had failed to open by 65 days of age in 3/8 animals. Although at 35 days of age the "TCB-Spinners" were markedly hyperactive during the dark phase of the daily light-dark cycle, this effect had disappeared by 65 days of age suggesting this change was sensitive to the maturation of the animal. The "TCB-Spinners" tended to be smaller than the control animals, but only the females were significantly smaller. Although the "TCB-Spinners" did not appear to have depressed neuromuscular reflexes, they did have a decreased grip strength, a greater difficulty in traversing a wire rod, and an increased latency in avoidance tests. By comparison, their escape latency when using electric foot shock and their orientation to environmental stimuli was not significantly different from that of controls. Tissue distribution studies indicated these effects were irreversible as no PCBs could be found in the tissues of adult spinners.

Chou et al. (1979) further characterized the "TCB-Spinner" syndrome in CD-1 mice, and investigated the effects of psychoactive drugs on spinner behavior. These researchers found the average litter size was decreased by TCB treatment, i.e. only about 60% of control litter sizes. The neonatal mortality was considerably higher than that of untreated animals, i.e. about 40% higher, and the body weights of spinners were only 75% of age-matched control mice. Because the dopaminergic system had been implicated by the observed changes in response to rotatory and locomotor activity, Chou et al. (1979) investigated the effects of several centrally-active drugs on the "spinning activity" of TCB-exposed animals. Chou and coworkers found that the higher doses of amphetamine (6-14 mg/kg) and apomorphine (5 mg/kg) decreased spinning behavior while lower doses of these drugs actually increased this activity. All test doses of both of these drugs increased the activity of control animals and the activity of "TCB-exposed Nonspinner" animals, but did not produce the spinner syndrome in this latter group. Haloperidol increased spinner activity at dosages of 0.1-0.5 mg/kg while 1.0 mg/kg completely abolished it. In contrast, all doses of haloperidol pretreatment decreased the activity of both control and "TCB-exposed Nonspinner" animals.

Chou's group also reported what they believed to be a unique histopathologic marker for the TCB-induced CNS injury that occurs during fetal development. The pathognomonic lesion representative of TCB exposure was the presence of cylindrical CNS peninsulas (CCPs) in spinal and cranial nerve roots. The link between this deficit and the spinning syndrome must be considered weak, however, because CCPs were also present in "TCB-exposed Nonspinner" mice. Yet based on the above evidence, the authors concluded that the evidence obtained in this study was suggestive of a neurochemical change in the dopaminergic system of the afflicted animals.

Agrawal et al. (1981) further elucidated the role the dopaminergic system plays in the "spinning" syndrome. Pregnant CD-1 mice were dosed with 32 mg/kg of 3,3',4,4'-tetrachlorobiphenyl on days 6-10 of gestation and the offspring of these dams were raised to one year of age. The weights of all TCB-exposed mice remained significantly lower than those of their age-matched controls, while motor activity ran significantly higher in the "spinner" group of TCB-exposed mice. When compared to control levels, dopamine levels of the corpus striatum were significantly lower in the "spinner" group. The "TCB-exposed Nonspinner" mice also tended to have lower dopamine levels, but the differences in this group were not statistically significant. Dopamine receptor binding of the corpus striatum was also found to be significantly decreased in all TCB-exposed animals, and "spinners" had the largest deficits. Thus, the authors concluded that the neurobehavioral changes induced by 3,3',4,4'-tetrachlorobiphenyl may, in part, be related to PCB-induced alterations in the dopaminergic system of the developing mouse.

Overmann et al. (1987) studied neurobehavioral and somatic effects of perinatal PCB exposure in rats. Pregnant rats were given diets containing 0.2 (no-dose control), 2.5, 26, or 269 ppm Aroclor 1254 from conception through weaning (day 21 post partum). Although no malformed fetuses were observed at any PCB dose level, maternal and fetal lethality was high in the 269 ppm treatment ,and pups from the lower dose treatments performed poorly on a battery of neurobehavioral tests and exhibited a dose-dependent decrease in pup birth weight. In the 26 ppm PCB treatment, pups showed delays in negative geotaxis, auditory startle, and air-righting reflex, and maximal electroconvulsive shock seizure was less severe compared to no-dose control animals. Pup liver weights at

birth and dam liver weights at weaning were increased by PCB treatment, while spleen and thymus weights were lowered and brain weights remained unchanged. Relatively high PCB levels were measured in the brains of PCB-treated dams (0.3-1.6 ppm) and pups at weaning (0.8-3.0 ppm) compared to untreated pup (0.04 ppm) and dams (0.03 ppm). Overmann et al. (1987) concluded that "maternal exposure to a high level of Aroclor 1254 severely affects rat reproduction and pup survival, while maternal exposure at lower levels can result in long-lasting neurobehavioral and somatic effects in the offspring".

The relevance of the observations by Overmann et al. (1987) to possible human perinatal PCB exposure is difficult to determine for several reasons. First, although the authors' measurement of surprisingly high PCB levels in the brain of pups and dams indicates that PCBs do pass the placental and blood:brain barriers, it is impossible to extrapolate this finding to any level of human exposure without the more useful and common PCB measurements in serum of adipose tissue. A second and perhaps critical factor acknowledged by the authors is the unclear contribution of polychlorinated dibenzofuran contaminants found in the Aroclor mixture utilized (10 ppb in the 269 ppm diet). Third, the significant neurobehavioral alterations in PCB-treated animals were observed almost exclusively at the 26 ppm PCB dose level, suggesting that low-dose exposures do not result in significant behavioral changes. In addition, the fact that significant changes in their measurements of negative geotaxis, auditory startle, and air-righting were not observed consistently (significant alteration frequencies were 2/4, 1/4, and 1/4 test days for the respective responses) casts doubt on the authors' suggestion that perinatal PCB exposure causes "persistent, probably irreversible functional changes in the nervous system." And finally, it is unknown how any of the small but significant changes seen in reflex behavior, particularly the duration of seizure following maximal electroconvulsive shock, might be related directly to any human reflex or higher behavior.

Wardell et al. (1982) have also conducted a teratological study in rats by administering the 3,3',4,4'-tetrachlorobiphenyl isomer at doses of 1, 3, or 10 mg/kg on days 6-18 of gestation. The two highest doses of this isomer produced a dose-dependent increase in embryolethality as well as other fetal changes which were described as blood in the amniotic fluid and damage to the fetal intestinal tract. However, as this particular PCB isomer is not a major component of

commercial PCB mixtures, and given the dosages needed to produce these changes (e.g. as compared to the LD_{50} of commercial PCBs), the relevance of these results with respect to the teratogenic potential of commercial PCB mixtures would appear to be limited. Rats have been studied for reproductive and neonatal effects a number of times, and in some of these investigations doses of up to 100 mg/kg per day for exposure periods of six months or more were used (Villeneuve et al., 1971a; Keplinger et al., 1972; Linder et al., 1974; Calandra, 1976; Gellert and Wilson, 1979; Vodicnik and Lech, 1980; Spencer, 1982). Although these studies have demonstrated some fetotoxicity and the fact that the dam may transfer acutely toxic levels of PCBs to the neonate via breastmilk, no teratogenic effects were noted in any of these other studies.

3.5.3 Other Studies

Earl et al. (1974) reported an abstract of studies performed in pigs and dogs that apparently have never been published as a full-length article. In these studies dogs received daily doses of 0.25, 1.0, or 5.0 mg/kg Aroclor 1254 from the day of breeding until the day they were necropsied. At the highest dose an increase in the number of resorptions, a decrease in litter size, and a reduced percentage of pup survival was reported. The terata observed in this report consisted of cleft palates, enlarged fontanelles, and superfluous phalanges. Casting doubt on these results, however, are the facts that 1) this dosage severely limited diet consumption (therefore the observed effects may have been the result of malnutrition), and 2) the authors' statement that the animals may have had a genetic defect that caused an unusually high incidence of terata. Further, review of the unpublished manuscript indicates that the abstract provides a somewhat misleading description of the studies, because the authors did not regard the two lowest doses as teratogenic for either species (Drill et al., 1982).

Earl et al. (1974) also reported observing syndactyly and cleft palates in swine at the 10 mg/kg dose and patent fontanelles and cleft palates at the 30 mg/kg dose. Again the highest dose reduced food consumption, and malnutrition may have contributed significantly to the findings. Concern for the possibility that the effects reported by Earl et al. (1974) are either the result of malnutrition or some genetic defect, or both, is raised by the fact that Hansen et al. (1975) failed to find any teratogenic effects in pigs exposed to PCBs.

Lundkvist et al. (1987) published a study examining the effects of perinatal Clophen A50 administration in guinea pigs. Clophen A50 (2 mg/animal/day) was administered orally during days 16-60 of gestation, and the animals were placed in metabolic cages to collect daily urine. Five of nine treated dams showed ruptured vaginal membranes 1-12 days before parturition accompanied by vaginal bleeding. The number of dead offspring was higher in the treated dams and the fetal-size estimates of gestational age of dead fetuses indicated that most fetal deaths occurred during days 32-46, but litter size and length of gestation were not altered significantly. Urinary estrone sulfate and 11-ketotetranor Prostaglandin F metabolite were both significantly elevated during days 47-60 of gestation in treated dams. The authors concluded only that they could not determine whether or not the observed changes in hormone excretion were due to fetal death in treated dams. Further conclusions from this study are also limited because the PCB dose used was extraordinarily high (2 mg/animal/day) in comparison to similar studies and only a single PCB dose was used.

Bowman et al. (1978) have reported the findings of a behavioral study performed in rhesus monkeys. This study consisted of three infants born to mothers who were exposed to dietary levels of 2.5 ppm Aroclor 1248 for 18-21 months. The PCB fat tissue levels of the three exposed infants were still 11-27 ppm at 10.5 months of age, but levels had decreased to 1.6 ppm or less by 23 months of age. The corresponding levels in control offspring were $\leq$ 0.3 ppm at both ages. Beginning at the age of four months and lasting until the animals were two years old, the ability of the monkeys to perform 11 different behavioral or learning tasks was evaluated. Based on the results of these tests, the authors stated this study had demonstrated that neonatal PCB exposure was associated with learning deficits. However, as can be seen in Table 3.5.4, there are a number of problems with the design of this study which severely limit any conclusions regarding whether or not PCB treatment had resulted in any adverse behavioral changes in these animals. For example, the lack of an adequate number of animals in the test (N=3) and control (N=4) populations is a serious and major flaw of this study. Second, after averaging the rank scores as has been done in Table 3.5.4, one finds that the "brightest" of the animals for all tests, i.e. that animal whose average ranking is closest to one, is actually a PCB-exposed animal. From this comparison it appears that not only was a PCB-treated animal the brightest

Table 3.5.4

PCB Exposure and Behavioral Scores in Rhesus Monkeys

Mean of Rankings (± standard deviation)	
PCB treatment group	Control group
2.7 ± 1.6	2.8 ± 1.4
5.4 ± 1.6	3.4 ± 1.6
6.1 ± 1.0	3.6 ± 2.0
	4.0 ± 2.2

Adapted from Bowman et al. (1978)

animal, but that the two "dumbest" animals in both the control and PCB-treated groups may not be significantly different from each other when all test scores are considered. Third, by providing only a ranking of the animal's performance, these data do not indicate whether the differences in the performance of an animal for any one test were significantly different from that of the other animals. Finally, given the apparent insensitivity and lack of objectivity of the test methods, it is not clear that the overall ranking of a particular animal is not merely an indication of the animal's native ability, rather than a test of behavioral deficits produced by chemical exposure. For the above reasons, it is the conclusion of this review that nothing meaningful regarding the possible behavioral effects of PCBs can be gleaned from this study.

Bowman and coworkers performed a more detailed analysis of locomotor data from this study and published it as a later report (Bowman et al., 1981). Control groups generally displayed lower overall activity, although the variability was substantial. Activity appeared to decline during successive sessions of measurement of locomotor activity in controls, but remained stable or increased in PCB-exposed offspring.

3.5.4 Summary of Teratogenicity Studies

Several studies have examined the teratogenic effects of PCB mixtures or single PCB congeners in mice and other species, with contradictory results. In these investigations, morphological or neurobehavioral effects have been studied as teratogenic endpoints. Although some studies are regarded by their authors as positive evidence of the teratogenicity of PCBs, maternal toxicity or limitations in the experimental design of these investigations, e.g. the doses of some of the isomers tested cannot be achieved with exposure to commercial PCB mixtures, severely limit the relevance of these findings.

Conflicting results regarding the effect of PCBs on the teratogenicity of TCDD have been obtained from two different studies. In one study, the incidence of TCDD-induced cleft palate in mice was enhanced by 2,3,4,5,3',4'-hexachlorobiphenyl but not by 2,4,5,2',4',5'-hexachlorobiphenyl. In the same study, 2,3,4,5,3',4'-hexachlorobiphenyl did not, however, increase the severity of TCDD-induced renal defects. In contrast, co-administration of a commercial PCB mixture, Aroclor 1254, with TCDD significantly reduced the incidence of cleft palate induced by TCDD alone.

Therefore, while there is evidence which suggests that certain hexachlorobiphenyl and tetrachlorobiphenyl PCB congeners are teratogenic in mice, there is no reasonable evidence that commercial PCB mixtures are teratogenic at doses not producing significant maternal toxicity or mortality.

3.6 GENOTOXIC EFFECTS OF PCBS

Tests measuring the genotoxicity of a chemical can be categorized in several different ways. The classification scheme is usually based on the type of genotoxic endpoint the test measures. Occasionally, the phylogenetic order of the test organism is also a part of the classification scheme. Genotoxicity tests may be further divided into *in vitro* and *in vivo* categories. Both isolated cells (*in vitro tests*) and whole animals (*in vivo* tests) are useful in determining the genotoxic potential of a chemical. The categorization scheme used in this Toxicant Profile is one similar to that considered by the International Agency for Research on Cancer (IARC), and is based on the type of endpoint the test measures regardless of the test organism being tested. Thus, investigations of the genotoxic potential of PCBs have been subdivided into tests measuring mutations, DNA damage, chromosomal damage (clastogenesis), dominant lethal tests, and cell transformation studies.

3.6.1 Bacterial Mutagenicity Studies

Tests measuring the mutation rate in bacteria are perhaps the most popular and widely used type of genotoxicity test. This popularity no doubt stems from their relative ease of use and the fact that they measure an actual mutation rather than some type of genetic damage which may or may not be repaired in the organism. This type of test usually incorporates a series of mutant strains of the bacterium that have lost their ability to synthesize a molecule of some importance to a particular cellular process. The deleted biochemical process is one which is easily identifiable. For example, the Ames assay developed by Dr. Bruce Ames uses various mutant strains of *Salmonella typhimurium* containing a mutation in a part of the genome responsible for the synthesis of histidine. In these strains of bacteria, histidine is a requirement for cell growth and these strains are therefore histidine-dependent. Mutations are easily scored in this test system as those colonies of bacteria capable of growing in histidine-deficient media. Bacteria able to grow in this medium must undergo a "backward mutation" to the wild type, i.e.

a histidine-independent form of the bacteria capable of synthesizing its own histidine.

Wyndham and coworkers (1976) were probably the first investigators to test chlorinated biphenyls or PCB mixtures in a bacterial test system. This study used the TA1538 mutant strain of *S. typhimurium* developed by Ames as the tester strain of bacteria. The Wyndham study was somewhat unusual, however, in that rabbit liver microsomes were added to metabolize the PCBs rather than the more typical use of an S-9 fraction from rat liver that has been induced by PCBs. The authors also failed to use a positive control to validate their test system. Contrary to the authors' finding that PCBs were weakly mutagenic under their stud conditions, the data provided in this paper does not support such claims. The first problem with the authors' contention of weak mutagenic activity is the fact that only 4-chlorobiphenyl and Aroclor 1221 demonstrated significant activity. Interestingly, Aroclor 1221, which has a chlorine content of 1.15 chlorine atoms per molecule and is therefore largely a monochlorobiphenyl mixture, was considerably less active than 4-chlorobiphenyl. This finding alone should have perhaps indicated to the authors that their results might not be consistent or reproducible. Concerning the results obtained for the other compounds tested and provided in this report, neither 2,2',5,5'-tetrachlorobiphenyl, Aroclor 1254, or Aroclor 1268 appear to have any mutagenic activity.

It is an unfortunate but not uncommon phenomenon in science that false positive or false negative data are generated and published in the literature. This appears to have been the case with the Wyndham et al. (1976) paper. Subsequent attempts by the senior author of this paper, Dr. Safe, to demonstrate that PCBs might cause mutations in bacterial test systems have failed. In an affidavit from Dr. Safe (Safe, 1980b), he has stated that based on his own inability to reproduce these findings of the previous study (Wyndham et al., 1976), 4-chlorobiphenyl should not be considered mutagenic. This would appear justified particularly since Schoeny (1982) has also tested 4-chlorobiphenyl and found it to be without mutagenic activity. Considering that 4-chlorobiphenyl was the more active of the two positive compounds reported in the Wyndham study, Aroclor 1221 should

Table 3.6.1

Summary of Microbial Mutagenicity Test Results

Tester Strain	*S. typhimurium*									*E. coil*		
Product	C3076	D3052	G46	TA98	TA100	TA1000	TA1535	TA1536	TA1537	TA1538	WP2	WP2uvrA
Aroclor 1221	—	—	—	—	—	—	—	—	—	Neg.	—	—
Aroclor 1254	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	—	Neg.	Neg.	Neg.	Neg.
Aroclor 1268	—	—	—	—	—	—	—	—	—	Neg.	—	—
Kanechlor 300	—	—	—	Neg.	Neg.	—	Neg.	Neg.	Neg.	Neg.	Neg.	—
Kanechlor 500	—	—	—	Neg.	Neg.	—	—	—	—	—	Neg.	—
2,5-tetra-chlorobiphenyl	—	—	—	Neg.	Neg.	—	Neg.	—	Neg.	Neg.	—	—
2,4-tetra-chlorobiphenyl	—	—	—	Neg.	Neg.	—	—	—	—	—	—	—
3,4-tetra-chlorobiphenyl	—	—	—	Neg.	Neg.	—	—	—	—	—	—	—
4-chlorophenyl	—	—	—	Neg.	Neg.	—	Neg.	—	Neg.	Neg.	—	—
2,4,6-hexa-chlorobiphenyl	—	—	—	Neg.	Neg.	—	—	—	—	—	—	—

Source: Levinskas (1981) and Schoeny (1982)

likewise not be considered to be a mutagenic substance (see Table 3.6.1). Therefore, it is the conclusion of this Toxicant Profile that Wyndham et al. (1976) were mistaken to identify 4-chlorobiphenyl and Aroclor 1221 as mutagens. Additional assays by other scientists also discount any suggestion that PCBs or monochlorobiphenyls are mutagenic in bacterial systems. Heddle and Bruce (1977; Bruce and Heddle, 1979) tested a number of different chemicals in the TA1535, TA1537, TA98, and TA100 strains of *S.typhimurium*, both with and without an S-9 fraction to provide a drug metabolizing system and possible activation of the compounds tested. Aroclor 1254 was not mutagenic in any of the tester strains of this study. Similarly, McMahon et al.(1979) reported results after screening a large number of compounds in a testing scheme which incorporated several auxotrophs of *S. typhimurium* and *E. coli*. The only chlorinated biphenyl tested was 4-chlorobiphenyl, but it was not mutagenic in any of the 10 bacterial strains used. Based on these studies and other reports in the literature (Schoeny et al., 1979; Schoeny, 1982; Rinkus and Legator, 1979; USEPA, 1980; Levinskas, 1981), all of which are summarized in Table 3.6.1, it is concluded that PCBs are not mutagenic in bacterial test systems.

3.6.2 Clastogenic/Chromosomal Damage Studies

Test systems measuring the clastogenic activity of a chemical are tests which measure some form of chemical-induced damage to chromosomes or a chemical-induced change in chromosomal number. Typically the types of change or damage are easily observed microscopically. The following paragraphs cite several studies demonstrating that PCBs lack the ability to damage or alter the chromosomes of rodent or human cells exposed under both *in vivo* and *in vitro* conditions.

Hoopingarner et al. (1972) have tested the genotoxicity of PCBs in human cells. In this investigation, human lymphocytes were stimulated with phytohemagglutinin to initiate cell division and then treated with 100 ppm Aroclor 1254 for the first 24 hours, again during the last eight hours of the S and G_2 stages of the cell cycle, and a third time during the three hours of mitosis. Cytological examinations of the cells during these stages of the cell cycle failed to reveal any effect of PCB treatment on chromosomal integrity. A finding of additional interest

reported in this study is the fact that 50 ppm of Aroclors 1260, 1254, 1248, 1221, and 1016 were all toxic to Chinese Hamster cells. Thus, it would seem likely that Hoopingarner et al. (1972) had examined the effects of PCBs on human lymphocyte chromosome integrity near or at cytotoxic doses.

Green et al. (1975a) tested Aroclors 1242 and 1254 for their ability to induce chromosomal damage in the bone marrow and sperm cells of rats. Aroclor 1242 was administered either in single doses of 1250, 2500, or 5000 mg/kg, or as four daily doses of 500 mg/kg; Aroclor 1254 was tested using three different dosages, i.e. 75, 150, or 300 mg/kg, which were administered daily for 5 days. The two highest doses of Aroclor 1254 and all of the doses of Aroclor 1242 caused a loss of body weight in these animals. The multiple doses of Aroclor 1242 were so high that they killed half of the test animals. In spite of the considerable systemic toxicity that was observed at these doses, neither Aroclor 1242 nor 1254 induced chromosomal damage in either sperm or bone marrow cells. Dikshith et al.(1975) also examined the effects of PCBs on rat cell chromosomes. These investigators exposed animals to dosages of 50 mg/kg/day of Aroclor 1254 for seven days. They reported finding no evidence of chromosomal damage in testicular sperm cells. The results of these two studies were later reproduced and substantiated by Garthoff et al. (1977). Male rats were fed dietary levels of 5, 50, or 500 ppm of Aroclor 1254 for five weeks after which sperm and bone marrow cells were examined for chromosomal damage. As in the previous studies, no evidence of chromosomal damage to either cell line was observed.

Several investigators have employed the micronucleus test as a measure of chromosomal damage. The micronucleus test measures chromosomal damage to red blood cells through the identification of chromatin fragments in erythrocytes. This assay takes advantage of the fact that chromosome fragments lacking a centromere are often left in the cytoplasm of one of the daughter cells when the nuclei are formed. These fragments become small cytoplasmic bodies within the cell and retain the staining characteristics of the chromatin material contained in the nucleus. But these chromatin-containing bodies are much smaller in size than the normal nucleus of a cell, hence the term micronucleus. Once any material containing chromatin has been stained, the chromatin bodies are easily visible and scored as a fragment remaining within the cytoplasm of the cell rather

than the nucleus. Because mature red cells lack a nucleus, those containing micronuclei are quite obvious, so these cells are often used for this test. This test is quite sensitive to the clastogenic effects of a chemical. For example, Heddle and Bruce (1977) examined newly-formed polychromatic erythrocytes from the bone marrow of C3HC57/F1 mice. In their version of the micronucleus test, an increase in incidence that was 1% above background was of high statistical significance. Although the dose administered was not reported in this article (it was published primarily as a review article listing the results obtained for various chemicals being screened by three different genotoxicity tests), Aroclor 1254 did not produce micronuclei. In a second report of what appears to be the same work, Bruce and Heddle (1979) indicated that four doses were tested. The highest doses used were typically the LD_{50}, or a dosage that was within a factor of two of the the LD_{50}. The remaining dosages were 1/2, 1/4, and 1/8 of the highest dose tested. Thus, the lack of clastogenic activity they report using the micronucleus test is significant because the experiment tested a dosage range which included the highest possible acute doses that might be given these animals. This work was also cited by Jensen and Ramel (1980) in their review and comparison of the micronucleus test as a short term screening tool for the prediction of a chemical's carcinogenic activity. The doses used in these studies (Heddle and Bruce, 1977; Bruce and Heddle, 197[illegible] also failed to induce sperm abnormalities believed to be indicative of mutations or chromosomal deletions.

Using the eukaryote test species *Drosophilia melanogaster*, neither of the French PCB mixtures Clophen 30 (approximate or equivalent to Aroclor 1242) nor Clophen 50 (equivalent to Aroclor 1254) produced chromosomal aberrations (Nilsson and Ramel, 1974).

Tazima (1980) failed to observe any mutagenic activity for Kanechlor 300 or Kanechlor 500 in a specific locus test unique for its use of the silkworm (*Bombyx mori*) as the test organism.

In conjunction with a study measuring the effects of PCBs on the breeding success of Ring Doves fed a 10-ppm diet of Aroclor 1254, Peakall et al. (1972) also reported on the observed incidence of chromosomal aberrations in the eggs of these birds. The average aberration rate changed from 0.8% in the control or untreated

birds to 1.8% in the PCB-treated birds. A single embryo irradiated with X-rays and serving as the positive control had an aberration rate of 18%. However, the average rate of chromosomal aberrations measured in the eggs of PCB-pretreated birds was only higher than the highest control value of 2% in 4/17 eggs coming from birds pretreated with PCBs. The frequencies in these eggs were 2.4%, 2.6%, 3.1%, and 9.4%. Thus, it is the consensus of this review, as it was the conclusion of the authors of this study, that these results are inconclusive. It is also noted that this dietary level led to almost complete reproductive failure in the second generation of birds.

In contrast, Aroclor 1242 has been injected into the eggs of White Leghorn chickens until PCB concentrations reached 20 ppm (Blazak and Marcun, 1975). Even though the concentrations used in this study caused early embryonic death and retarded development, evidence of chromosomal aberrations was not observed.

3.6.3 Dominant Lethal Tests

A dominant lethal test is a measure of germ cell mutations, or possibly chromosomal damage, that is so severe in nature that the changes are lethal to the developing embryo. Dominant lethal mutations may be measured as a decrease in viable offspring, or alternatively as an increase in resorption frequency. This test is normally performed by dosing only the males with the chemical in order to rule out the possibility of maternal toxicity as a contributing and therefore confounding factor.

Green et al. (1975b) reported that Aroclor 1242 administered as single doses of 625, 1250, and 2500 mg/kg or after five daily dosages of 125 or 250 mg/kg failed to induce dominant lethal mutations in the rat. Aroclor 1254 administered for five days at dosages of 75, 150, or 300 mg/kg or at dietary levels of 25 or 100 ppm for 70 days was likewise without effect.

Mice have also been studied. Keplinger et al. (1972) and Calandra (1976) tested Aroclors 1242, 1254, and 1260 in mice at dosages of 500 or 1000 mg/kg and found these to be without dominant lethal effects.

3.6.4 DNA Damage Studies

On the basis of sedimentation rates, Stadnicki et al. (1979) have reported that the epoxide of tetrachlorobiphenyl caused single-stranded chromosomal breaks in the DNA of L-929 cells at concentrations ranging from 1 µg/ml to 100 µg/ml. A mixture of two hydroxylated metabolites, and to a much lesser extent tetrachlorobiphenyl, was reported to have caused some damage at 20 µg/ml and what was reported as significant damage at 100 µg/ml. The significance of this single *in vitro* test is questionable given the fact that the epoxide metabolite was the only chemical species demonstrating a strong activity in this test system. This conclusion is reached in part because the authors, on the basis of this study, similarly concluded that the epoxide metabolite is the only chemical species of interest with regard to its potential carcinogenicity. This conclusion is also supported by the earlier work of Hoopingarner et al. (1972), who demonstrated 50 µg/ml of most Aroclors was cytotoxic. By not performing tests to examine cell viability, Stadnicki et al. (1979) apparently failed to account for the possibility that the results observed may be due to cytotoxicity rather than genotoxicity. Moreover, all mammalian tests of mutagenicity or genotoxicity, as well as those *in vitro* tests containing some activation system, were negative. These results indicate that even if the epoxide metabolite is actually genotoxic, sufficient quantities of this metabolite are not generated under *in vitro* or *in vivo* conditions to create a genotoxic effect.

3.6.5 Cell Transformation Studies

Pienta (1980) reported that Aroclor 1254 did not induce cell transformations after eight days of incubating Syrian hamster embryo cells in concentrations as high as 50 µg/ml (50 ppm). This dose was shown to be cytotoxic in the Hoopingarner et al. (1972) study and was five times the highest dose later used by Norback et al. (1981). Norback et al. (1981) reported that Aroclor 1254 transformed C3H10T11/2 cells to Type III foci after six weeks of continuous exposure to 10 µg/ml (10 ppm) of Aroclor 1254; cells exposed to 1 µg/ml were not transformed. Cells exposed to Aroclor 1254 at concentrations of 10 ppm for 24 hours also failed to induce foci. The authors suggested that these results indicate that the effects of PCBs in cell culture may include promotion.

3.6.6 Summary of Genotoxicity Studies

The results of the preceding studies have been summarized in Table 3.6.2. The only test clearly reported as positive (Stadnicki et al., 1979) is of questionable relevance, raising the question of how this study should be scored in Table 3.6.2. The authors of this Toxicant Profile have decided to acknowledge this study as a citation of positive activity only because this test has not been specifically refuted. However, a question mark next to the scoring indicates the dubious value of this particular citation to the determination of the genotoxicity of PCBs. After considering the number of times PCBs have been tested in a reasonable battery of genotoxicity or mutagenicity tests and found to be without activity, and the fact that the tests selected measure several different critical endpoints of genotoxicity, the opinion of this review is that there is no scientific evidence of significant genotoxic activity for commercial grade PCB mixtures. It is also concluded that these studies demonstrate that PCB-induced liver tumors observed in rodents most probably occur by an epigenetic mechanism.

Table 3.6.2

Summary Table of the Genotoxicity of PCBs

	Type of Genotoxic Activity			
Species	DNA damage	Mutation	Chromosomal damage	Cell Transformation
Prokaryotes	Neg.(28/12)	Neg.(2/2)		
Mammalian cells *(in vitro)*	Pos.?(1/1)		Neg.(6/9)	Neg.(2/2)
Mammal *(in vivo)*			Neg.(3/3)	
Human cells *(in vitro)*			Neg.(1/1)	

The first number in the parentheses indicates the total number of times an Aroclor was tested; the second number in parentheses indicates the total number of times a specific test strain or cell line was tested. Thus, the results followed by the larger numbers in parentheses represent the results most likely to be reproduced if further testing is performed in the future.

3.7 CARCINOGENICITY

3.7.1 Studies in Mice

Nagasaki et al. (1972) initially examined the hepatocarcinogenic effects of Japanese brands of PCB fluids by feeding male mice dietary levels of 100 ppm, 250 ppm, and 500 ppm for 32 weeks. As this particular citation represents only a short communication, detailed discussions of the experimental design and histopathological examinations of this investigation were lacking. An increased incidence of liver tumors was found in only one of the treatment groups, those mice receiving the 500 ppm diet of Kanechlor 500, where hepatomas were identified in 58% or 7/12 of the animals. The livers from animals in this group also contained nodular areas and many necrotic foci. In sharp contrast to these findings, no hepatomas and none of these histopathologic changes were observed in animals receiving lower doses of Kanechlor 500 or in any of the animals receiving Kanechlor 400 or Kanechlor 300.

The results of the above study also appear to have been reported in two other publications under Ito et al. (1973a&b). As in the previous study, it was reported that male mice of the dd strain were fed diets containing Kanechlor 300, Kanechlor 400, or Kanechlor 500 at dietary levels of 100, 250, or 500 ppm for 32 weeks. PCBs significantly increased the liver weights of the animals, and at the highest dose of Kanechlor 500 the liver:body weight ratio had increased 3-fold. Histopathological examination of the livers revealed focal hypertrophy in the centrilobular hepatocytes in the space between the sinus endothelium and the hepatocytes. Another change observed in all PCB treatment groups, except those receiving 500 ppm of either Kanechlor 500 or 400, was a marked amyloid degeneration of the liver. For some reason, the liver tumors in these more recent publications (Ito et al., 1973a&b) have been reclassified and the tumors reported as hepatomas in the previous communication (Nagaski et al., 1972) were now listed as carcinomas (Ito et al., 1973a&b). Nodular hyperplasia, rather than hepatoma, was now reported in 7/12 animals (58.3%), and 5/12 of the livers (41.7%) were re-classified as having well-differentiated hepatocellular carcinomas. The carcinoma cells were reported to be comprised of irregularly shaped cells with pyknotic nuclei and the occasional

occurrence of mitotic nuclei. The reason for changing the classification of these neoplasms from hepatoma to carcinoma is not provided. Of some interest to discussions of the carcinogenic potential of PCBs is the fact that all of the other doses of all three Kanechlors tested failed to produce even nodular hyperplasia. Thus, the tumorigenicity reported was quite specific for the dose and the chlorine content of the Kanechlor being tested.

The results of these experiments also appear to have been reported later by Nagasaki et al. (1974) in a paper discussing the effects of various factors on the carcinogenesis of PCBs and benzene hexachloride in mice. The discussion provided here is based on a translation of the original publication. Two hundred male and female dd strain mice were fed diets containing 100, 250, or 500 ppm of either Kanechlor 300, Kanechlor 400 or Kanechlor 500 for a total of 32 weeks. All diets appear to have increased the liver weights of the male mice, although no statistics were provided in this paper to substantiate this interpretation. The liver weights of female mice appear to have been increased by all diets at PCB concentrations of 250 ppm or greater. As can be seen in Table 3.7.1, the highest dietary level of Kanechlor 500 produced an increase in nodular hypertrophy and in hepatocellular carcinoma in male animals. In contrast, few histopathologic changes were observed in the livers of female mice. In particular, there was a lack of amyloid degeneration, which was evident in most male livers, and unlike the male animals no hepatocellular carcinomas were noted at the highest dose of Kanechlor 500. No tumors or metastases were found in other organs in either sex. Thus, the carcinogenicity of PCBs in these experiments was specific for chlorination, dose, and sex of the animal.

Kimbrough and Linder (1974) examined the effects of PCBs in mice and obtained results consistent with those found for the lesser-chlorinated Kanechlors of the preceding study. Groups of 50 male Balb/cJ mice were fed 300 ppm Aroclor 1254 for either eleven months or for six months followed by a five-month recovery period. The authors pointed out that this dietary level was some 2,500 times the Food and Drug Administration's estimate of the average human daily PCB intake

Table 3.7.1

Histopathological Findings In Mice Fed Various Dietary Levels of Kanechlors 300, 400 and 500

PCBs in diet (ppm)	Oval cell/ Bile duct proliferation	Hepato-cellular hypertrophy	Amyloid degeneration	Nodular hyperplasia	Hepatocellular carcinoma
Male Animals					
Kanechlor 500					
500 ppm	+	++	30%	53%	7/17 (41%)
250 ppm	±	+	15%	0%	0/20 (0%)
100 ppm	-	+	28%	0%	0/18 (0%)
Kanechlor 400					
500 ppm	+	++	5%	0%	0/20 (0%)
250 ppm	±	+	21%	0%	0/19 (0%)
100 ppm	-	±	65%	0%	0/17 (0%)
Kanechlor 300					
500 ppm	+	+	10%	0%	0/20 (0%
250 ppm	-	±	32%	0%	0/19 (0
100 ppm	-	±	74%	0%	0/19 (0%)
Controls	-	-	0%	0%	0/20 (0%)
Female Animals					
Kanechlor 500					
500 ppm	-	+	0%	24%	0/17 (0%)
250 ppm	-	±	0%	0%	0/20 (0%)
100 ppm	-	-	5%	0%	0/19 (0%)
Kanechlor 400					
500 ppm	-	+	0%	0%	0/17 (0%)
250 ppm	-	±	0%	0%	0/20 (0%)
100 ppm	-	±	0%	0%	0/20 (0%)
Kanechlor 300					
500 ppm	-	±	0%	0%	0/20 (0%)
250 ppm	-	±	0%	0%	0/20 (0%)
100 ppm	-	-	0%	0%	0/19 (0%)
Controls	-	-	0%	0%	0/12 (0%)

Adapted from Nagasaki et al. (1974)

from food during the early 1970's. About one-half of the animals in each PCB treatment group died during the first four months, but this problem seems to have been unrelated to PCB treatment since control animals suffered a similar incidence of mortality. Of the 22 mice surviving the 11-month feeding study, all animals exhibited hepatomegaly, and PCB treatment had increased the liver:body weight ratio from the 5.8% measured for the control animals to approximately 25%. Adenofibrosis (i.e. cholangio- fibrosis) was observed in all 22 livers taken from mice fed PCBs for 11 months. However 13/68 livers taken from control animals had occasional, small areas of necrosis and fibrosis. Of the livers taken from animals receiving 300 ppm Aroclor 1254 for 11 months, the nuclei were enlarged, hyperchromatic, and atypical. The cytoplasm was either smooth or vacuolated, and the Kupffer cells contained a brown pigment. Some of these livers had extensive necrosis and fibrosis. In each of the livers, several areas of hepatocytes had been replaced by proliferating epithelial cells which formed ducts and often produced mucus. In addition to these histological changes, 10 hepatomas were found in nine of these livers. The tumors were described as well-circumscribed and surrounded by compressed parenchyma or strands of fibrosis. In the 24 surviving mice fed PCBs for only six months followed by a five month recovery period, only one liver contained a hepatoma. Yet, liver fibrosis was observed in two-thirds of these animals and hepatocellular necrosis was evident in most of the livers.

3.7.2 Studies in Rats

Kimura and Baba (1973) exposed 10 male and 10 female Donryu rats to a variable dietary level of Kanechlor 400 for 400 days. The diet initially contained 38.5 ppm and was fed to the animals for four weeks; the dietary level was then doubled for the following eight weeks; the initial dietary level was then increased 4-fold for three weeks; it was then increased 8-fold for another three weeks; finally it was increased to 16 times the initial level for three more weeks. This last increase in the dietary levels of PCBs (a level that was approximately 616 ppm) was found to be too toxic and caused a considerable weight loss in the animals. In response to the toxicity observed at this dose, the dietary level was reduced to 462 ppm for the remaining 32 weeks of the study. Further complicating interpretations of this

study is the fact that animals died or were sacrificed at various times throughout the experiment; therefore the total PCB dose each animal received may differ. In general, the total amount ingested was thought to be 1300-1800 mg for the group of male animals and 1100-1500 mg for the female animals. Microscopically, the livers of all of the treated animals contained fatty degenerative changes, and while 6/10 of the livers from female animals had adenomatous nodules, none of the livers of the male animals contained such nodules. However, the liver nodules observed in the female animals do not appear to be related to the PCB treatment as 2/5 (40%) of the livers from the control female animals also contained adenomatous nodules.

In a second study, Kimura et al. (1976) fed 12 female Donryu rats diets containing 400 ppm Kanechlor 400 for six months. The estimated dose corresponded to a total of 531 mg of PCBs during this period. Eight of the 12 animals were then sacrificed 590 days after the feeding began. None of these animals developed hepatocellular carcinoma, and 9/12 of the livers were normal in appearance, suggesting that the degenerative changes observed in the previous study are reversible.

Ito et al. (1974) fed male Wistar rats Kanechlor 300, Kanechlor 400, or Kanechlor 500 at dietary levels of 100, 500, or 1,000 ppm for up to 52 weeks. No hepatocellular carcinomas were found in the livers of any of the PCB-treated rats (see Table 3.7.2). The highest dose of all three Kanechlors did produce a cholangiofibrosis of the liver, but this effect was not observed at lower doses in any of the Kanechlors. Nodular hyperplasia was observed in 30-40% of the rats exposed to the two highest doses of Kanechlor 500 (i.e. doses of 500 ppm and 1,000 ppm) and in animals receiving a diet containing 1,000 ppm of Kanechlor 400. Oval cell proliferation and proliferation of the bile duct cells were observed in all treatment groups. Hypertrophy of the centrilobular cells was also evident in animals receiving the highest dose of the two most heavily-chlorinated PCB mixtures. Fatty changes and fibrosis were also observed in the livers of animals of several of the treatment groups. The fatty changes, hypertrophy, and fibrosis of the liver all tended to be present and correlate with the observation of nodular hyperplasia, suggesting that these changes may have been contributory factors.

Table 3.7.2

Histopathological Findings in the Livers of Wistar Rats Fed Various Levels of Kanechlors 300, 400 and 500

PCBs in diet (ppm)	Oval cell/ Bile duct proliferation	Fatty changes	Hepato-cellular hypertrophy	Fibrosis	Cholangio-fibrosis	Nodular hyperplasia
Kanechlor 500						
1000 ppm	+	+	++	±	4/13(30%)	5/13(39%)
500 ppm	+	+	+	-	0/16(0%)	5/16(31%)
100 ppm	±	±	±	-	0/25(0%)	3/25(12%)
Kanechlor 400						
1000 ppm	+	±	++	++	2/10(20%)	3/10(30%)
500 ppm	±	-	+	-	0/8(0%)	0/8(0%)
100 ppm	±	-	+	-	0/16(0%)	2/16(13%)
Kanechlor 300						
1000 ppm	+	+	+	-	2/15(13%)	0/15(7%)
500 ppm	±	±	+	-	0/19(0%)	0/19(0%)
100 ppm	±	±	±	-	0/22(0%)	1/22(5%)
Controls	-	-	-	-	0/18(0%)	0/18(0%)

Adapted from Ito et al. (1974)

Kimbrough et al. (1975) published the first major positive study demonstrating that Aroclor 1260 can produce hepatocellular carcinoma in the rat. In this study 200 female Sherman strain rats were fed Aroclor 1260 at a dietary level of 100 ppm for approximately 21 months. There was a statistically significant 6-7% decline in the weight gain of the animals exposed to PCBs in this study suggesting that the dose used approximated the maximally-tolerated dose. The histopathological findings from this study are summarized in Table 3.7.3. The most consistent histopathologic difference in the PCB treatment group was the finding of hyperplastic or neoplastic nodules in 144/184 (78%) of the livers. More important, however, was the finding of hepatocellular carcinoma in 26/184 (14%) of

the PCB-treated animals. The tumors were well-differentiated neoplasms of the trabecular type, except in three of the animals which had tumors with a glandular, papillary pattern. Foci of coagulative necrosis were occasionally observed in the cancerous areas, but there was no fibrosis or other evidence of chronic degenerative changes. Tumors in areas other than the liver were not listed as significantly different. However, in some cases there was a substantial decrease in the tumor incidence of other tissues, e.g. as in the case of parafollicular cell tumors of the thyroid. Furthermore, the total incidence of tumors was not changed by PCB treatment. The total incidence of all tumors in the control population was 135/173 (78%) while the incidence in the PCB-treated animals was 135/184 (73%). In other words, the PCB-induced increase in liver tumors was offset by a decreased incidence of extra-hepatic tumors in Aroclor 1260-treated animals of 110/183 (60%) compared to an extrahepatic tumor incidence in control animals of 134/173 (77%). The Aroclor 1260 diet was also without adverse effect on the life-span of the animals. In fact, about twice as many control animals had died for various reasons before the experiment was terminated at 23 months than had PCB-treated animals (Kimbrough et al., 1975).

In 1978 the National Cancer Institute examined the carcinogenic potential of Aroclor 1254 (NCI, 1978). Groups of 24 male and 24 female Fischer rats were fed Aroclor 1254 at dietary levels of 25, 50, or 100 ppm for 105 weeks. Clinical signs of toxicity including hair loss, facial edema, and cyanosis occurred by week 72 in the high dose animals and the mean body weights were roughly only 2/3-3/4 that of their respective controls. This decrease in body weight exceeds the no more than 10% weight loss guideline for the estimated maximally-tolerated dose that is part of the NCI guideline for cancer bioassays (NCI, 1979). The clinical signs noted in the high-dose group by week 72 and in the mid-dose group by week 104 were alopecia, amber-colored urine, facial edema, exophthalmos, and cyanosis. In addition to the clinical evidence of toxicity in these animals, a decrease in the survival of the male animals showed a significant dose-related trend. Several histopathologic changes occurred in the livers of animals receiving PCBs that appeared to be related to the PCB treatment, particularly the incidence of

Table 3.7.3

Results of Carcinogenesis Bioassay of Aroclor 1260

Organ/Tissue	Lesion Type	Tumor Incidence: Control Animals	Tumor Incidence: Aroclor 1260 Animals
	Incidence of Other Pathological Changes		
Liver	Neoplastic nodules	0/173	144/184
	Areas of cytoplasmic alteration	28/173	182/184
	Tumor Incidence		
Liver	Hepatocellular carcinoma	1/173	26/184
Thyroid gland	Parafollicular cell tumor	37/160	18/166
Adrenals	Pheochromocytoma	1/173	1/167
Pituitary gland	Chromophobe adenoma	41/153	28/139
"	Carcinoma	0/153	1/139
Uterus	Endometria polyp	18/149	25/163
"	Adenocarcinoma	0/149	2/163
"	Sarcoma of endometrial stroma	3/149	7/163
Urinary bladder	Papilloma	1/167	0/169
Salivary gland	Fibrosarcoma	1/173	0/184
Lung	Adenoma	2/173	2/184
tissue	Lipoma	0/173	2/184
Brain	Glioma	0/173	2/184
Ovary	Granulosa theca cell tumor	5/149	0/163
"	Papillary adenoma	1/149	2/163
Mammary gland	Fibroadenoma	17/173	13/184
"	Adenocarcinoma	5/173	1/184
Blood	Granulocytic leukemia	1/173	0/184
"	Lymphoma	0/173	0/184
Kidney	Hemangioma	0/173	1/184
Thymus	Thymoma	1/173	0/184
Parathyroids	Adenoma	0/173	2/184
Skin	Fibroma	0/173	1/184
Total Tumor Load		135/173	135/184
(% = total tumors/N)		(78%)	(73%)
Extrahepatic Tumor Load		134/173	110/184
(% = extrahepatic/N)		(77%)	(60%)

Adapted from Kimbrough et al. (1975)

hyperplastic nodules and adenomas (see Table 3.7.4). Male animals had two hepatocellular carcinomas in the 100 ppm group, one in the 50 ppm group, and none in the group fed 25 ppm. No such tumors were observed in the female animals at any dietary level of Aroclor 1254. Although the incidence of these tumors was not significant, the observed incidence of non-neoplastic hyperplastic nodules did appear to be dose-related. These proliferative lesions were similar in appearance to what was termed at this time "focal areas of cellular alteration" if classified using the scheme proposed by Squire and Levitt (1975).

Table 3.7.4

Summary of the Hepatic Lesions in Fischer 344 Rats Following the Chronic Administration of Aroclor 1254

	Male Animals			Female Animals		
Lesion	25 ppm	50 ppm	100 ppm	25 ppm	50 ppm	100 ppm
Number of Animals Necropsied	24	24	24	24	24	24
Nodular Hyperplasia	5	8	12	6	9	17
Adenomas	0	0	1	0	1	2
Hepatocellular carcinoma	0	1	2	0	0	0

Adapted from NCI, 1978

The foci of these hyperplastic nodules generally involved two or more hepatic lobules, occasionally contained severely vacuolated hepatocytes, and in some instances small foci of basophilic hepatocytes. The adenomas were characterized as involving several swollen lobules of severely vacuolated hepatocytes, but these cells still maintained the general sinusoidal structures of normal hepatic lobules.

The summary of this report noted that although there was no statistically significant increase in the incidence of cancer in any tissue, the incidence of nonneoplastic heperplastic nodules appeared to be dose-related. These data were also reviewed by the Data Evaluation/ Risk Assessment subgroup of the Clearinghouse on Environmental Carcinogens, a group responsible for providing peer review of NCI studies. The primary reviewer noted that with regard to the liver pathology caused by PCBs in the rat, once the proliferative stimulus was removed the hyperplastic nodules regress and disappear. This reviewer felt that the animal data indicated Aroclor 1254 may act like a tumor promoter and not a complete carcinogen, and the following conclusion was adopted by the subgroup :

> *It is concluded that, under the conditions of the bioassay, Aroclor 1254 was **not carcinogenic** in Fischer 344 rats; however, a high incidence of hepatocellular proliferative lesions in both male and female rats were related to treatment. In addition, the carcinomas of the gastrointestinal tract may be associated with treatment in both males and females. Based on the liver proliferative lesions in the treated rats and published reports, it is suggested that Aroclor 1254 may be a tumor promoter.*

Morgan et al. (1981) have taken the same tissue sections that originated in the NCI bioassay (NCI, 1978), stained the stomach sections for alkaline phosphatase, and then re-sectioned these tissues for further histological evaluation. The overlap between pathologic evidence of a lesion and alkaline phosphatase (AP) activity was incomplete. For example, in the 100 ppm group 63% of the lesions were at sites of focal AP activity while 25% were located in regions of diffuse AP activity and 13% were in areas which had no detectable level of AP activity. The final incidence of intestinal metaplasia was 6.4% in controls, 8.3% in animals fed 25 ppm Aroclor 1254, 10.4% in the 50 ppm group, and 31.3% in the 100 ppm animals (see Table 3.7.5). Intestinal metaplasia was not found in any of the eight animals that died before the 73rd week of the experiment. Although this number is small, it suggests that this type of lesion occurs late in the life of the animal, and no correlation was found between early deaths and the incidence of stomach lesions. Additionally, no correlation was found between the incidence of stomach lesions and liver lesions in the animals. The stomach lesions were most often noted in the pyloric region of the stomach and duodenum (88% of all lesions

Table 3.7.5

Incidence of Stomach Lesions in Rats Chronically Fed Aroclor 1254 : A Re-Evaluation of the NCI Study

Dose level	Animals per group	Intestinal metaplasia	(%)	Adenocarcinoma	(%)
0 ppm	47	3	(6.4%)	0	(0%)
25 ppm	48	4	(8.3%)	1	(2.1%)
50 ppm	48	5	(10.4%)	3	(6.3%)
100 ppm	48	15	(31.3%)	2	(4.2%)

Adapted from Morgan et al., 1981

were found in these areas), suggesting a toxicity specific to the cells of these areas. Gastric adenocarcinomas comprised six of the 33 total lesions identified in these slices. Three were found in tissues from the 50 ppm treatment group and two in the animal group fed 100 ppm. Thus, the incidence of this lesion did not appear to be a dose-related change. The authors concluded that the actual number of stomach lesions they believed should have been observed in the G.I. tract tissue sections of the NCI study was twice the number of lesions reported in the original NCI study. On the basis of their findings, the authors of this paper further concluded that chronic oral Aroclor 1254 exposure leads to the induction of intestinal metaplasia in the Fischer 344 rat, and probably leads to induction of adenocarcinoma of the glandular stomach (Morgan et al., 1981).

Ward (1985) has also published a review of the slides originating from the NCI bioassay. In addition to the aforementioned dose-related depression of body weight, Ward (1985) also discusses, in some detail, the substantial decrease in animal survival that occurred in this study. While the survival rate in control animals and in the treatment group receiving 25 ppm was 92% and 85%, respectively, only 58% of the animals receiving the 50 ppm diet and 46% of the animals fed diets containing 100 ppm survived to the end of the bioassay. Focal hyperplasia was of the eosinophilic type and was only observed in PCB-treated animals. According to his own classification scheme, if compression was found

on two sides of the foci, Ward diagnosed the lesion as hepatocellular adenoma. Based on his diagnosis of the NCI bioassay slides, Ward identified a total of 13 eosinophilic, basophilic, or vacuolated adenomas of the liver (see Table 3.7.6). All of these occurred, with one exception, in those animals fed the two highest dietary levels of Aroclor 1254 and the occurrence of adenomas was slightly greater in the male animals (8/13). In contrast to the findings of the NCI (1978) report, Ward reported finding only two liver carcinomas, and both occurred in male animals receiving the 100 ppm diet. Ward (1985) also reported that Aroclor 1254 increased the incidence of intestinal metaplasia and gastric adenocarcinoma. As in his

Table 3.7.6

Summary of the Hepatic Lesions Reported by Ward Following His Review of the NCI Bioassay*

	Male Animals			Female Animals		
Lesion	25 ppm	50 ppm	100 ppm	25 ppm	50 ppm	100 ppm
Number of Animals Necropsied	24	24	24	24	24	24
Adenomas	1(0)	2(0)	5(1)	0(0)	3(1)	2(2)
Hepatocellular Carcinoma	0	0(1)	2(2)	0(0)	0(0)	0(0)

* Numbers in parentheses indicate the findings of the NCI study

Adapted from NCI, 1978

earlier study with Morgan and Hartman (Morgan et al., 1981), the change in adenocarcinoma was neither significant at any treatment level nor dose-related. A significant increase in intestinal metaplasia was only observed in the 100 ppm dose group. Thus, the Ward (1985) study is relatively consistent with the previous NCI (1979) bioassay. No statistically significant increase in liver cancer or cancer of other tissues was observed, but the 100 ppm dose did result in significant

intestinal metaplasia. Ward mentions the fact that the liver lesions he observed were predominantly of the eosinophilic type rather than the basophilic type generally observed in the control animals. Based on these changes Ward proposes the idea that these data may suggest that PCBs are capable of initiating liver tumors rather than promoting the background tumor incidence. Yet, in contradiction to this suggestion, Ward also makes note of the fact that inducing agents like PCBs and phenobarbital cause a proliferation of the smooth endoplasmic reticulum (SER) of the liver. Since a proliferation of the SER gives rise to an eosinophilic appearance of the cytoplasm, the liver hypertrophy and induction of microsomal enzymes associated with PCB exposure provides an obvious explanation for the basophilic to eosinophilic change Ward noted in the cellular appearance of the liver tumors of PCB-treated animals.

Schaeffer et al. (1984) used a total of 432 weanling Wistar rats to examine the effects produced by chronically feeding rats Clophen A60 (equivalent to Aroclor 1260) or Clophen A30 (similar in composition to Aroclor 1242; Brinkman and DeKok, 1980). The study consisted of three groups: Group 1, a control group of 1 animals receiving the normal diet; Group 2, with 152 animals receiving a diet containing 100 ppm of Clophen A30; and Group 3, which consisted of 141 animals fed a diet containing 100 ppm of Clophen A60. After day 801 animals were randomly selected and killed, and the experiment was terminated on day 832. The Clophens used in this study were reported to be free of any chlorinated dibenzofuran contamination, but the level of detection for this analysis was not specified. Those animals that died before day 800 were necropsied, and hepatocellular carcinomas were only identified in the PCB treatment groups and were first observed after 700 days. One was found in Group 2 and a total of 9 were identified in Group 3. This latter number was statistically significant for the Clophen A60 treatment, but represented a liver cancer incidence of only 7% for the entire group. In contrast, the incidence of thymoma was significantly reduced by PCB treatment, declining from 12% in the control group to 3-4% in the treatment groups. Likewise, the total number of the remaining types of neoplasms was significantly reduced by the PCB treatment, with Clophen A60 causing the greatest reduction (from 52 in controls down to 18 in the Clophen A60 group). The results up to day 800 of this experiment are provided in Table 3.7.7.

Table 3.7.7

Most Frequently Occurring Lesions in Animals Necropsied up to Day 800

Lesion	Controls	Clophen A30	Clophen A60
Number of animals not dying	131	138	129
Number necropsied	78	51	44
(% necropsied)	60%	37%	33%
Hepatocellular carcinoma	0	1	9*
Thymoma	16	4*	2*
Other neoplasias	52	28*	18*

Adapted from Schaeffer et al., 1984
* denotes significance ($p<0.05$)

The results for the animals still alive after 800 days, i.e. those animals randomly selected, killed, and necropsied on days 801-832, are provided in Table 3.7.8. The liver cancer incidence was significantly elevated, but only in those animals receiving the Clophen A60. Therefore, the results of this study were consistent with previous rat studies in that a commercial PCB mixture of 60% chlorine content was reported to have induced hepatocellular carcinoma, but a lesser-chlorinated PCB mixture was not carcinogenic. The Schaeffer et al. (1984) study also confirmed another finding of the Kimbrough et al. (1975) study, i.e. chronic PCB treatment was associated with a significant decrease in the incidence of extra-hepatic tumors.

Of additional interest was the temporal progression of the liver lesions listed as preneoplastic lesions (foci of hepatocellular alterations), neoplastic nodules, and hepatocellular carcinoma. As can be seen in Table 3.7.9, all of these lesions occurred to some extent in control animals and were primarily a feature of older

Table 3.7.8

Most Frequently Occurring Lesions in Animals Necropsied on Days 801-832

Lesion	Controls	Clophen A30	Clophen A60
Hepatocellular carcinoma (%)	1/53 (2%)	3/87 (3%)	52/85* (61%)
Thymoma (%)	9/53 (17%)	12/87 (14%)	0/85* (0%)
Other neoplasias (%)	19/53 (36%)	33/87 (38%)	13/85 (15%)
Nephritis (%)	21/53 (40%)	7/87* (8%)	0/85* (0%)

Adapted from Schaeffer et al., 1984
* Denotes significance ($p<0.05$)

Table 3.7.9

Frequency of Hepatocellular Alterations Induced by Chronic Feeding Studies with Clophen A30 and Clophen A60

Time Interval	# of Foci	Neoplastic Nodules	Hepatocellular carcinoma
		Control Animals	
301-400	0%	0%	0%
401-500	11%	0%	0%
501-600	8%	8%	0%
601-700	6%	12%	0%
701-800	5%	0%	0%
801-832	32%	4%	2%
		Clophen A30	
301-400	0%	0%	0%
401-500	0%	0%	0%
501-600	55%	0%	0%
601-700	33%	17%	0%
701-800	50%*	5%	5%
801-832	49%	40%*	3%
		Clophen A60	
301-400	0%	100%	0%
401-500	0%	0%	0%
501-600	40%	60%	0%
601-700	0%	100%	0%
701-800	3%	67%*	30%*
801-832	0%*	40%*	61%*

* Denotes a significant difference from the control value ($P<0.05$)
Adapted from Schaeffer et al. (1984)

animals (i.e. > 500 days old). Clophen A30 did increase the incidence of foci and neoplastic nodules, but this effect tended to occur very late in the life of the animal and did not progress to hepatocellular carcinoma. In contrast, after 500 days of exposure there was a rapid progression from foci to neoplastic nodule and finally hepatocellular carcinoma in those animals fed Clophen A60. This complete loss of foci in these animals after day 600, and the progressive shift from foci to nodule and then carcinoma might be interpreted as a promotional effect induced by Clophen A60.

In a letter to the editor, Young (1985) comments on several interesting and important aspects of the Schaeffer et al. (1984) study that received little attention by from its authors. Young's analysis of these data focused on the effects of PCB exposure on tumor incidence in liver, on tumor incidence in extra-hepatic tissues, and on mortality. The tables generated by Young (1985) are provided in Table 3.7.10. Young points out that the Schaeffer et al. (1984) study actually demonstrated three things. These are: 1) that a significant increase in hepatocellular carcinoma occurred only in the animals receiving Clophen A60, 2) that PCB treatment resulted in a significant decrease in other neoplastic lesions, and 3) that PCB treatment significantly increased the chances of survival of the animals.

Given these findings, Young states that after careful consideration it is difficult to conclude, given the balance of the data, whether or not PCB treatment was in fact detrimental to the rats. That is, typically we would not consider a treatment detrimental if it significantly enhanced the rate of survival and significantly decreased the total tumor load of the exposed rats. In essence then, he questions the human relevance of tumors which occur only very late in the life of the animal, are not life-shortening and do not metastasize to other organs of the body. To quote Young:

> *Usually, carcinogenic studies are terminated at some arbitrary point, such as two years. Some have argued that the dire consequences of tumors would occur if the animals were allowed to live. Here the animals were allowed to live out their life-span and, on balance, the animals in the treated groups benefited as measured by total tumor load and longevity.*

If the purpose of long-term studies is to extrapolate to humans, then one finds it difficult to infer dire consequences to humans when the treatment is beneficial in the model system. Is the model only useful for inferring bad events? The model should be equally valid for detrimental and beneficial effects.

Finally, the analysis of Young also calls into serious question a suggestion made by Schaeffer et al. (1984), that the decrease in the incidence of thymoma might be caused by immunosuppressive effects of PCBs. While PCBs cause thymic atrophy at certain doses, any proposed immunosuppressive effect cannot be considered to have a significant clinical impact when the treated animals did not ultimately suffer a greater incidence of morbidity or mortality from either infectious diseases or the cancer induced by this treatment.

Norback and Weltman (1985) fed 70 male and 70 female Sprague-Dawley rats a diet containing 100 ppm Aroclor 1260 for 16 months followed by a reduction to 50 ppm for the next eight months. The animals were then fed a control diet for the remaining five months of their lives. All results were compared to a control group which initially consisted of 126 animals, 63 of each sex. At various time points throughout this study two control animals of each sex and three PCB-treated animals of each sex (10 animals in total) were anesthetized with ether and the medial left lobe of the liver of each animal was surgically removed. These tissue samples were taken at 1, 3, 6, 9, 12, 15, and 18 months. At 24 months a similar group was killed and at the end of 29 months all remaining animals were sacrificed. The induction of liver hypertrophy in the centrilobular area of the lobule was evident at the first observation period, made one month after the PCB diet was initiated. By the 18th month the liver:body weight ratio had increased from 4% to 12% in the female animals. Macroscopically these investigators noted evidence characteristic of neoplastic nodules near the capsular surface, hepatocellular carcinomas, and adenofibrosis. In the PCB-exposed group, the observed lesions appeared in the following sequence: centrilobular hypertrophy at one month, foci of cells at three months, foci of altered cells in the centrilobular and midzonal regions at six to nine months, neoplastic nodules at 12 months,

Table 3.7.10

The Incidence of Hepatocellular Carcinoma, Other Neoplastic Lesions and Mortality by Time Period

Time Interval (days)	Treatment Group		
	Control	Clophen A30	Clophen A60
	A. Hepatocellular Carcinoma		
301-400	0/137	0/150	0/135
401-700	0/111	0/122	0/115
701-800	0/92	1/107	9/85*
	B. Other Neoplasms		
301-400	0/137	1/150	2/150
401-700	32/111	11/122*	9/115*
701-800	30/92	15/107*	7/85*
	C. Incidence and Percentage(%) of Mortality		
101-400	2/139 (1.4%)	2/152 (1.3%)	3/141(2.1%)
401-700	45/137(32.8%)	43/150(28.7%)	23/138(16.7%)
701-800	39/92 (42.4%)	20/107(18.7%)	30/85 (35.3%)
1-800	86/139(61.9%)	65/152(42.8%)*	56/141(39.7%)*

* Different from control value ($p<0.05$), χ^2

Adapted from Young (1985)

trabecular carcinoma after 15 months, and adenocarcinoma at 24 months. Simple cystic cholangioma and adenofibrosis appeared in animals 18-23 months after the exposure began. There was no evidence of metastases to the lungs. All trabecular carcinomas had cell arrangements with a glandular, ductal, or cystic pattern and all adenocarcinomas had some elements of the trabecular pattern of growth. The lumens of the adenocarcinomas were the apparent result of cellular necrosis. The incidence of tumors in animals 18 months or older are presented in Table 3.7.11. It should be remembered that seven to eight animals sacrificed after 18 months, i.e., at least 15% of the group of animals in which late developing tumors were observed, had undergone a partial hepatectomy during the first 18 months. The effect of this cannot be determined from this experiment, but partial hepatectomy has been used as a promotional stimulus to increase the incidence of liver tumors induced by other carcinogens. Therefore, it is unfortunate that the authors did not note or describe the possible influence that this might have had on the final tumor incidence measured.

Another important factor to consider which is not readily apparent from Table 3.7.11 is that almost all of the tumors reported in this study were very late-developing tumors. In Table 1 of this paper, only four trabecular carcinomas and only two adenocarcinomas had developed by the time of the 18- and 24-month sacrifices (see Table 3.7.12). Thus, 35/41 or some 87% (39/45) of the liver tumors observed in this study developed in the last 25-29-month period of the study. Furthermore, there is a notable sex-related difference in the response to Aroclor 1260. Only two male animals developed liver tumors, a number (4%) which most probably is not significantly different from the control group. In contrast, 96% of the tumors observed in these animals occurred in the females, and 91% were not identified until the 29-month sacrifice. These tumors had not metastasized to other organs, and none appear to have been life-shortening. Concerning this last aspect, unfortunately no information is given describing the cause of death for any animals dying early, or revealing the number of animals lost. But from the data supplied it would appear that a number of early deaths occurred only in the group of male control animals.

Table 3.7.11

Incidence of Hepatocellular Neoplasms

	Incidence or % Tumors Observed (The actual number of animals with tumors)		
	Male	Female	Total
A. Control Animals	**(N=32)**	**(N=49)**	**(N=81)**
Trabecular carcinoma	0%(0/32)	0%(0/49)	0%(0/81)
Adenocarcinoma	0%(0/32)	0%(0/49)	0%(0/81)
Number negative	100%(32/32)	98%(48/49)	99%(80/81)
B. Aroclor 1260 Animals	**(N=46)†**	**(N=47)††**	**(N=93)**
Trabecular carcinoma	4%(2/46)	40%(19/47)	23%(21/93)
Adenocarcinoma*	0%(0/46)	51%(24/47)	26%(24/93)
Neoplastic nodule only	11%(5/46)	4%(2/47)	8%(7/93)
Number negative	85%(39/46)	4%(2/47)	44%(41/93)

† The total number includes 8 animals that had received a partial hepatectomy during the first 18 months.

†† The total number includes 7 animals that had received a partial hepatectomy during the first 18 months.

* Animals with both trabecular carcinoma and adenocarcinoma were placed only in the adenocarcinoma group.

Adapted from Norback and Weltman (1985)

Table 3.7.12

Temporal Development of the Hepatocellular Neoplasms Identified in the Norback and Weltman Study

Time Interval	Neoplastic Nodule	Trabecular Carcinoma	Adenocarcinoma
	Male Animals		
1 month	0	0	0
3 months	0	0	0
6 months	0	0	0
9 months	0	0	0
12 months	0	0	0
15 months	0	0	0
18 months	0	0	0
24 months	1	0	0
29 months	5	2	0
	Female Animals		
1 month	0	0	0
3 months	0	0	0
6 months	0	0	0
9 months	0	0	0
12 months	1	0	0
15 months	3	1	0
18 months	3	2	0
24 months	3	2	2
29 months	2	19	24

Adapted from Norback and Weltman (1985)

These same observations were also noted by the authors, who stated in the discussion of this paper:

> *Although the tumors met the morphological criteria for malignancy, their biologic behavior was relatively unaggressive. The neoplasms did not metastasize to distant organs nor invade blood vessels. Mortality of the animals was not increased. The lack of greater morbidity or mortality is likely due to slow progression of the neoplastic process and late appearance and slow growth of the hepatocellular carcinoma.*

The authors further noted that it remains to be established whether PCBs have an initiating effect or whether the neoplasms observed result from the promotion of a background incidence of initiated cells.

Rao and Banerji (1988) recently reported the results of a study in which male Wistar rats were fed Aroclor 1260. Groups of 32 rats were fed 0, 50, or 100 ppm of Aroclor 1260 in a 10% protein diet apparently over a 120 day interval (although in the discussion section of the paper the exposure period is mentioned as 28 weeks). Survival and body weight gain were not affected by Aroclor treatment. Liver histopathology included adenofibrosis, neoplastic nodules, bile duct proliferation, and necrosis of individual liver cells. The incidence of neoplastic nodules in 0, 50, and 100 ppm groups was 0/32 (0%), 24/32 (75%), and 16/32 (50%), respectively. No carcinomas were reported. The results of this study indicate that neoplastic lesions can be induced by Aroclor 1260 treatment after a relatively short period of time in the male Wistar rat. However, it is not possible to determine whether or how many of these lesions would progress to carcinomas. Because the incidence of neoplastic nodules was greater in the group of rats fed 50 ppm Aroclor 1260 than the 100 ppm group, the authors suggest that their data indicate a greater potential for carcinogenicity at lower doses of Aroclor. In view of the short time span of their study, the apparent absence of carcinomas in any group, and the positive dose-response relationships suggested in more extensive studies, more definitive studies would be required to reach this conclusion.

3.7.3 Studies In Other Species

Calandra (1976) reported, in summary form, a carcinogenicity bioassay performed in dogs. Groups containing four male and four female dogs were fed 1, 10, or 100 ppm of Aroclors 1242, 1254, or 1260 for two years. No remarkable findings were reported; however, this exposure interval is considerably shorter than the lifetime of the species being tested.

3.7.4 Interactions Between PCBs and Carcinogens

The interactive effect of PCBs with carcinogenic chemicals has been the subject of many investigations. Since PCBs are not genotoxic, many of these studies were conducted in an attempt to identify these chemicals as potential promoters of tumorigenesis. From the reviews of these studies, it is clear that PCBs affect the carcinogenic activity of selected genotoxic chemicals. What is not certain, however, is the tendency toward any clear trend of PCB-enhancement or prevention of chemical carcinogenesis. The effect of PCBs on the tumorigenicity of diverse chemical carcinogens has been tested using many experimental designs. Perhaps the most critical factor in determining how PCBs will influence the carcinogenicity of a chemical is the relationship between the time of exposure to PCBs and the carcinogen. Depending upon the time of administration, whether prior to, during, or after exposure to a chemical carcinogen, PCBs may enhance or decrease the tumorigenic effect of the chemical. The varying effects of PCBs on chemical carcinogenesis are discussed in the following studies.

3.7.4.1 Studies Finding A Positive PCB Promotion of Chemical Carcinogenesis

Pereira et al. (1982) examined Aroclor 1254 as a possible promoter of diethylnitrosamine-induced altered foci in the livers of male Sprague-Dawley rats. In this study, rats received a single oral dose of diethylnitrosamine (DEN) (0.3 mmol/kg body weight) 24 hours after a 2/3 partial hepatectomy. Seven, 28, and 49 days after DEN treatment, a 500 mg/kg dose of Aroclor 1254 was administered by intraperitoneal injection. For purposes of comparison, a known promoter of

tumor growth, phenobarbital, was administered to another group of rats in the drinking water at a concentration of 500 ppm. Groups of animals were killed on day 28, 49, and 70 after DEN treatment and the livers examined for gamma-glutamyl transpeptidase (GGTase) positive foci. Phenobarbital-treated animals were killed on day 59. GGTase-positive foci were considered to be putative indicators of hepatic carcinogenesis. Examination of rats receiving DEN and only one dose of Aroclor (animals killed 28 days after DEN treatment) had a mean of 2.28 GGTase-positive foci per cm^2 of liver. Controls which received only DEN had significantly less GGTase-positive foci (0.70 foci/cm^2). Rats receiving two doses of Aroclor (animals killed on day 49) also had greater numbers of foci than animals treated only once with DEN (3.47 foci/cm^2 versus 0.98 foci/cm^2). The mean number of foci in rats treated with a third dose of Aroclor was the same as that for rats receiving only two injections and was not significantly different from animals receiving DEN only, which were killed on the day 79. It is noted that phenobarbital treatment induced at least twice the number of GGTase-positive foci (7.06 foci/cm^2) as any of the Aroclor-treated animals after a latency period of only 56 days. While these results appear to suggest that Aroclor 1254 may shorten the latency period for the development of DEN-induced altered foci, the results for high doses of PCBs were less dramatic than those achieved by the drug phenobarbital, which appeared to enhance the total number and shorten the latency period. Furthermore, the dosages of PCBs used in these experiments were excessive; as previously discussed, the LD_{75} for a 43 day observation period in rats has been reported to be 500 to 2,000 mg/kg (Tucker and Crabtree, 1970). Thus, the revelance of these data remain open to question.

Preston et al. (1981) examined the tumor promoting capability of purified Aroclor 1254 and Aroclor 1254 which contained polychlorinated dibenzofurans (PCDF) to investigate the question of whether PCDF contaminants in PCB mixtures are required for tumor promotion. Sprague-Dawley rats in treatment groups II,IV, and VI were exposed to diethylnitrosamine (DEN) in drinking water at a concentration of 66 μg/ml for five weeks. Group II rats received only DEN treatment, while groups IV and VI were also fed diets containing 100 ppm purified Aroclor 1254 or PCDF-contaminated Aroclor 1254 (Arochlor 1254 + PCDF)

for 18 weeks following DEN treatment. Groups III and V were treated with diets containing 100 ppm Aroclor 1254 or Aroclor 1254 + PCDF only. Groups II, III, and VI contained 40 rats while group I (controls) contained 80 rats. All animals were sacrificed at 23 weeks and their livers examined for foci of cellular alteration, neoplastic nodules, hepatocellular carcinomas, chloangiosarcomas, and cholangiomas. The results of this examination are presented in Table 3.7.13.

Table 3.7.13

Influence of Aroclor 1254 With and Without Polychlorinated Dibenzofurans on Diethylnitrosamine Tumorigenesis

Group	No. of rats	Hepatocyte lesions		
		Foci of cellular alteration	Neoplastic nodules	Hepato-cellular carcinoma
I	72	0	0	0
II	32	10	6	5
III	34	0	0	0
IV	33	0*	10	21*
V	34	0	0	0
VI	32	1*†	5†	27*†

Group I, control; Group II, DEN only; Group III, AR 1254 only; Group IV, DEN + AR 1254; Group V, AR 1254-PCDF; Group VI, DEN + AR 1254-PCDF.

* significantly different from group II ($p < 0.05$)
† not significantly different from group IV ($p < 0.05$)

Adapted from Preston et al. (1981)

The incidence of hepatocellular carcinomas was significantly elevated by both PCB groups, i.e., DEN plus purified Aroclor 1254 (group IV) or DEN plus Aroclor 1254 + PCDF (group VI), over the group receiving DEN alone (II). No hepatocyte lesions or biliary lesions were found in livers of rats from groups treated with Aroclor 1254 (III) or Aroclor 1254 + PCDF (V) alone. The authors suggested that these results indicated that PCBs alone were capable of promoting tumor formation and that

PCDF contaminants were not required for Aroclor 1254 to promote tumorigenesis.

Ito et al. (1978) investigated the promoting effect of several chemicals, including PCBs, on the production of hyperplastic liver nodules in Fischer rats. Unfortunately, the mixture of PCBs supplied by the Kanegafuchi Chemical Co. was never specifically defined. For this reason, interpretation of the results of this study is limited. Rats were fed a diet containing 200 ppm 2-acetyl aminofluorene (2-AAF) for two weeks followed by 1000 ppm PCB in the diet for eight weeks. Rats were sacrificed in the tenth week of the experiment and the livers examined for hyperplastic nodules. The number of hyperplastic nodules/10 cm^2 liver for 2-AAF alone and 2-AAF + PCBs were 0.0 and 1.6, respectively.

Anderson et al. (1986) examined the promoting effect of Aroclor 1254 ir neonatal Swiss mice treated with the initiator N-nitrosodimethylamine (DMN). Male mice were treated with a single intraperitoneal dose of DMN (5 mg/kg) on the fourth day of life followed by a 50, 250, or 500 mg/kg intragastric dose of Aroclor 1254 four days later. Animals were killed 16 or 28 weeks after the Aroclor dose. The effect of PCB treatment on DMN-induced liver alterations was complex. At 16 weeks PCB treatment seemed to have increased the number of detectable proliferative lesions in the liver. However, at 28 weeks all animals administered PCBs had fewer hepatic lesions than did animals treated only with DMN. At this time interval a significant negative correlation between PCB dose and the number of animals with tumors was observed. In the lung there was a significantly greater incidence of lung tumors in those mice treated with DEN + 500 mg/kg PCBs compared to mice treated with DMN alone at both the 16 and 28 week sacrifices. Lung tumor incidences in the 50 mg/kg and 250 mg/kg PCB-treated animals were not significantly different from mice treated with only DMN. However, the relevance of results obtained with the highest PCB dosage is open to question as the acute LD_{50} in mice is only about 2,000 mg/kg. Thus, it appears that these studies add no new information to those promotion studies already considered.

Buchmann et al. (1986) investigated the promotional effect of

3,3',4,4'-tetrachlorobipheyl (TCB) and 2,2',4,4',5,5'-hexachloro- biphenyl (HCB) in rats treated with diethylnitrosamine (DEN). Female Wistar rats were treated with 50 ppm DEN in the drinking water for 10 days and were allowed to recover for 10 days. Following the recovery period, rats were treated with weekly doses of 150 μmol of TCB or HCB for eight weeks. Rats were killed one or nine weeks after the last PCB treatment and the livers examined for ATPase activity. ATPase-deficient islets were used as a marker for preneoplastic liver lesions. One week following the final PCB dose, the number and volume of ATPase-deficient islets for TCB- and HCB-treated animals were significantly greater than for animals treated with DEN alone. An even greater effect was observed at 19 weeks. Animals treated with TCB had significantly greater numbers and volume of ATPase-deficient islets than animals treated with HCB. TCB was found to preferentially induce MC_1 and MC_2 isozymes of cytochrome P-450 while HCBP induced isozymes PB_1 and PB_2.

Mazue et al. (1983) investigated the promotional effect of PCBs (unspecified type) in male Fischer 344 rats. Rats were fed 0.02% 2-acetylaminofluorene (2-AAF) in the diet for 10 weeks and were allowed two weeks to recover. Rats were then fed 250 or 500 ppm PCB for 25 to 48 weeks. The only results reported for this study were plasma gamma-glutamyltransferase (GGTase) activities. Plasma GGTase levels in rats treated with 250 ppm and 500 ppm PCB were approximately 60 IU/l and 150 IU/l, respectively. Rats treated with 2-AAF had GGTase levels of approximately 15 IU/l. The results of this study were presented in a unique way. Other investigators have generally reported hepatic GGTase rather than plasma GGTase levels, therefore it is difficult to compare the results of this study with other studies of PCB promotion.

Arai et al. (1983) examined the promotional effects of PCB (type unspecified) on dimethylnitrosamine (DMN)-induced liver and kidney tumors in male Fischer 344 rats. Rats were fed 0.04% DMN for two weeks, followed by two weeks on a normal diet. Rats were then fed PCBs (500 ppm) for 28 weeks. In addition to PCB treatment, one group was also unilaterally nephrectomized during week five of the experiment. DMN + PCB-treated animals had a 91% incidence of liver nodules, 14% incidence of cholangiofibrosis, and 14% incidence of hepatocellular

carcinomas. Animals treated with only DMN had a 28% incidence of liver nodules. Cholangiofibrosis or hepatocellular carcinomas were not observed in these animals. PCB treatment appeared to decrease the incidence of nephroblastoma in rats. Rats treated with DMN had a 94% incidence of nephroblastoma, whereas animals given DMN + PCB had a 36% incidence of nephroblastoma. No other differences were clearly discernible since the authors failed to statistically analyze their data. It thus appears that PCBs may promote DMN-induced liver tumorigenesis but protect against DMN-induced kidney tumorigenesis.

Oesterle and Deml (1983) investigated the promoting effect of PCBs on the development of putative preneoplastic, enzyme-altered islands in livers of weanling and adult female Sprague-Dawley rats. Rats were given nitrosamines and Clophen A50 by gastric intubation. Weanlings were given a single dose of 8 mg/kg of diethylnitrosamine or 9.1 mg/kg of 4-nitrosomorpholine (both dissolved in water). Adult rats were given dosages of 8 mg/kg per day of diethylnitrosamine for 12 consecutive days. Each group (weanlings and adults) received Clophen A50 (100 mg/kg of body weight) once weekly for one to seven weeks. PCB treatment was started one week after the last application of nitrosamines. In adults, the application of diethylnitrosamine increased the number and area of ATPase-deficient islands for a period of six weeks. But by week 12 both of these parameters had decreased, showing one-sixth the number and one-third of the area when compared with the data obtained after six weeks. Application of Clophen A50 to these adults did not alter island number or area until week six. However, from week six to ten, the number of islands persisted and there was a slight increase in both parameters rather than the expected decrease. From weeks 10 to 12, the number and area of enzyme-altered islands had increased significantly to some 30-fold of the expected values. In weanlings, both diethylnitrosamine and 4-nitrosomorpholine caused an increase in the number and area of enzyme-deficient islands following the initiation of nitrosamine treatment. This effect did not reverse after six weeks. Additional treatment with Clophen A50 significantly enhanced both the number and area of enzyme-deficient islands from week 4 to 12, compared with the corresponding data obtained with

either diethylnitrosamine or 4-nitrosomorpholine. This enhancement in number and area after 12 weeks was two-fold and eight-fold respectively. In both groups, initiation of islands by Clophen A50 was low and was also significantly lower than that of both nitrosamine treatment groups. Oesterle and Deml (1983) concluded that Clophen A50 enhances (promotes) the yield of preneoplastic islands initiated with nitrosamines.

Deml et al. (1983) examined the effects of various combinations of PCB administration before and after administration of benzo[a]pyrene. Clophen A50 was administered either as a single dose (500 mg/kg of body weight) before, or in repeated dosages (50 mg/kg of body weight, given once weekly for 10 consecutive weeks) after a 200 mg/kg dose of benzo[a]pyrene. These investigators reported that, while body weights were not affected by treatment with PCBs or benzo[a]pyrene, liver weights of PCB-treated animals were significantly increased when compared to those of benzo[a]pyrene-treated animals. In addition, PCB treatment (single dose of 500 mg/kg Clophen A50) resulted in an approximate 80-fold increase in aryl hydrocarbon hydroxylase activity. However, treatment with a single dose of benzo[a]pyrene did not produce any enzyme-altered (ATPase-deficient or GGTase-positive) islands. When Clophen A50 was administered either before or after benzo[a]pyrene, a few islands resulted to which no significance was attributed. However, a 3-fold increase in the number of islands was observed in animals treated with PCBs both before and after benzo[a]pyrene administration. Apparently, the average area per island was not affected by this latter treatment. The investigators concluded that PCB pretreatment resulted in the induction of benzo[a]pyrene metabolism with the formation of reactive intermediates of benzo[a]pyrene, which induced liver damage. The fact that the lesions initiated by benzo[a]pyrene became apparent only when PCBs were administered after benzo[a]pyrene indicated that PCBs act as promoters.

Oesterle and Deml (1984) demonstrated a dose-dependent promoting effect of PCBs on enzyme-altered islands in livers of adult and weanling female Sprague-Dawley rats. Weanling rats were treated with a single dose of 8 mg/kg of diethylnitrosamine via gastric intubation. Adult rats were treated with 8 mg/kg of

diethylnitrosamine per day for 12 consecutive days. One week after the last dose of diethylnitrosamine, rats received dosages of 2, 10, 25, 50, or 100 mg/kg of Clophen A50, once weekly for seven consecutive weeks. Thereafter, animals were kept without further treatment until 12 weeks after the start of the experiment. No differences in the body weight were found between the PCB-treated animals and controls. Macroscopic examination of the livers from PCB-treated animals revealed no alterations. Liver weights and liver-to-body weight ratios were enhanced after application of Clophen. In adults, the promoting effect of Clophen A50 was dose- dependent. Application of 2, 10, 25, 50, or 100 mg PCB once a week for seven consecutive weeks caused a 2-, 4-, 5-, 10-, and 12-fold increase in the number of ATPase-deficient islands and a 2-, 5-, 7-, 8-, and 12-fold increase in island area, respectively. Similarly, there was a dose-dependent increase in the number and total area of GGTase-positive and glycogen-storing islands in the dose range of 2 to 100 mg/kg Clophen A50. The percentage of islands with coincidence of the three markers increased with increasing doses of Clophen A50: from 11% in diethylnitrosamine-treated animals up to 74% after additional application of 100 mg of the PCB mixture. In weanlings, application of 2 mg/kg of Clophen A50 was ineffective as a promoter. Administration of higher doses, however, resulted in a significant and dose-dependent increase in the number and area of ATPase-deficient, GGTase-positive, and glycogen storing islands. The percentage of islands with coincidence of the three markers amounted to 18% in nitrosamine-treated rats and 67% in those animals treated with diethylnitrosamine and 100 mg/kg of Clophen A50.

Evaluation of a dose-response relationship and of a no-effect level is important since PCBs are ubiquitous in the environment. Oesterle and Deml (1984) concluded that, considering the data presented in their investigation, under normal conditions a promoting effect in humans due to PCB exposure seems unlikely. This conclusion was based on the facts that the normal human ingestion of PCBs is generally much lower than the doses applied in the their experiments and that no causal link between deaths due to neoplasms and PCBs in Yusho patients (who received dosages of ~0.03-0.15 mg/kg of body weight) has been identified. This exposure is in the range of the lowest dose used in the present

experiment (average daily intake of 0.29 mg/kg of body weight), which was ineffective as a promoter in adult rats.

Similar results and conclusions were obtained by Greim et al. (1984, 1985a &b). Following initiation with a single oral dose of 8 mg/kg of N-nitrosodiethylamine, weanling female Sprague-Dawley rats were given a 0.1 to 50 mg/kg dosage of Clophen A50 by gavage three times a week for 11 weeks. The animals were sacrificed 12 weeks after initiation and the numbers of ATPase-deficient and GGTase-positive islands were observed. Additionally, the dose-dependent induction of aldrin epoxidase activity and cytochrome P-450 content was also measured. Whereas the higher doses (5-50 mg/kg PCB) significantly increased the number of preneoplastic islands, no such effect was observed with dosages of 1 mg/kg PCB or below. A positive correlation between enzyme induction, amount of cytochrome P-450, and promoting effect was found with PCB dosages greater than 2 mg/kg of body weight. No effect on enzyme induction was observed with PCB dosages of 1-2 mg/kg of body weight. Greim et al. (1985a&b) concluded that this again suggests a no-effect level in the promoting effect by PCBs, and that determination of the activity of hepatic microsomal enzymes can be used to establish effective promoting doses of PCB. Their results suggest that PCB-promotion is linked with enzyme induction and that, because the low daily ingestion of PCBs in the general population (5 to 10 µg PCB/day) does not result in enzyme induction, tumor promotion by PCBs in the general population is unlikely.

Deml and Oesterle (1987) examined the promoting effects of Clophen A-50 on weanling female Sprague-Dawley rats following initiation with nitrosamine. Rats received a single 8 mg/kg of body weight dosage of diethylnitrosamine. One week following the oral administration of nitrosamine, Clophen A-50 was administered three times a week for 11 weeks. The PCB dosages used were 0.1, 0.5, 1, 5, or 10 mg Clophen A-50/kg of body weight. Twelve weeks following the initiation of the experiment, the livers were screened histochemically for preneoplastic lesions (ATPase- deficient, GGTase-positive, and glycogen-storing islands). As was seen in previous studies (Oesterle and Deml, 1984; Greim et al., 1984, 1985a), there was

a dose-dependent promoting effect of Clophen A-50, and this effect could be shown with all markers tested. Doses below 1 mg PCB/kg of body weight showed no promoting effect. However, there was a significant increase in the ATPase-deficient, GGTase-positive, and glycogen-storing islands at dosages between 1 and 10 mg Clophen A-50/kg of body weight. The authors concluded that the average human daily intake of PCBs (5-10 μg/day) would not result in a promotional effect in humans since this daily intake is 1,000-fold lower than the lowest effective promoting dose in rats.

Shelton et al. (1984a) fed rainbow trout diets containing 100 ppm of Aroclor 1242 or 1254 in combination with 1100 ppm diethylnitrosamine (DEN) for one year. Hepatocellular tumor incidence for rainbow trout fed 1100 ppm DEN, 1100 ppm DEN + 100 ppm Aroclor 1242, and 1100 ppm DEN + Aroclor 1254 for a year were 10.2%, 40.2%, and 21.6%, respectively. In contrast with results from another study in which the authors (Shelton et al., 1984b) observed PCB-induced (Aroclor 1254) reduction of hepatic tumors resulting from aflatoxin B-1 treatment, PCBs enhanced the tumorigenic effect of the initiating agent DEN. The two experimer. differed with respect to initiating agent and doses of PCB used; these factors are possible reasons for the contrasting results. Interestingly, lower doses of Aroclor 1254 (50 ppm) were used in the aflatoxin study (Shelton et al., 1984b), which resulted in a reduction in tumor incidence.

Brunn et al. (1987) examined the promoting ability of PCBs on diethylnitrosamine-induced liver tumorigenesis in laying hens. Four treatment groups were administered DEN (10 mg/kg, im) alone either once (DEN 1x) or twice (DEN 2x) weekly for up to 300 days, and a second group of hens was given DEN twice weekly with Clophen C (approximately 5 mg/kg/day, given as 100 mg/kg diet) or the same dietary level of Clophen C alone. Serial sacrifices (1 animal per treatment) were made of "representative animals" at various time intervals after treatment began and various histological preparations of liver tissue were examined. Glycogen-rich cells apparently lacking nuclei and staining acidophillic were noted in DEN-only treatments and basophillic, alkaline phosphatase negative, and GGT positive foci were observed in all DEN-treated

chickens; each of these characteristic foci were characterized as preneoplastic by the authors. These preneoplastic foci occurred approximately 60 days earlier in the DEN 2x treatment group compared to the DEN 1x treatment group; however, these lesions were not seen when Clophen C was given alone or with DEN 2x. Although PCB treatment alone increased lethality, no preneoplastic or neoplastic hepatic lesions were observed. PCB treatment plus DEN 2x appeared to shorten the time of the first observation of neoplastic hepatic lesions by about 40 days, and reportedly increased the total tumor yield of all chickens by about 2-fold compared to DEN 2x alone. The authors concluded that the histopathological changes seen with PCBs plus DEN in chickens is similar to that observed previously in rats and that Clophen C seems to be co-carcinogenic with DEN.

Certain aspects of the findings by Brunn et al. (1987) cast doubt upon their conclusion of PCB co-carcinogenicity with DEN. First, it is clear from their study that Clophen C did not cause tumors alone, yet it is also clear that the PCB dose was not tolerated well by the animals (as evidenced by 25% lethality occurring in the PCB-only treatment group). The authors did not report on the chronic toxicity of feeding such high levels of PCBs in the diet, which might include weight loss and malnutrition. Second, their methodology in assessing time-to-tumor lacks credibility, since the definition of "representative animals" is certainly ambiguous and a shortened time-to-tumor in the PCB/DEN treatment is based upon histological examination of only one chicken sacrificed one time interval (three to four weeks) before the appearance of tumors in the DEN 2x treatment. Third, it appears unexplainable that preneoplastic lesions were not seen in the PCB/DEN 2x animals, yet tumors reportedly developed faster and in greater frequency and size than DEN 2x alone. And fourth, the significant differences in tumor size and frequency with PCB treatment appeared to result from the examination of a few chickens having livers fully permeated with tumors, where the DEN 2x tumor yield was 285 g/3 chickens and the PCB/DEN 2x tumor yield was 365 g/3 chickens. Therefore, when one considers the toxicity of the PCB dosage, the unexplained lack of preneoplastic lesions in PCB-treated chickens, and inadequate methodolgies used, the authors' conclusion that PCBs are co-carcinogenic is only weakly supported and obviously unclear.

Loury and Byard (1983) demonstrated that Aroclor 1254 (500 mg/kg of body weight) given four days prior to the isolation of rat hepatocytes dramatically increased unscheduled DNA synthesis *in vitro* in hepatocytes treated with four potent mutagens. They concluded that, on the cellular level, PCB induction of cytochrome P-448 was the mechanism responsible for the potentiation of the hepatocellular genotoxicity of the tryptophan and glutamic acid pyrolysate mutagens.

Ozawa et al. (1985) investigated the effectiveness of S-9 preparations from livers of rats treated with 3,4,5,3',4'-pentachlorobiphenyl (PenCB) or 2,4,5,2',4',5'-hexachlorobiphenyl (HexCB) in activating the promutagens benzo[a]pyrene, 2-amino-6-methyldipyrido[1,2-a:3',2'-d] imidazole (Glu-P-1), 3-amino-1,4-dimethyl-5H-pyrido[4,3-b] indole (Trp-P-1), and aflatoxin B-1 (AFB-1) in the Ames assay. They treated male Wistar rats with single intraperitoneal doses of 1.5 µmol PenCB/kg, 55 µmol HexCB/kg, 150 µmol 3-methylcholanthrene/kg, or 700 µmol phenobarbital/kg and sacrificed the animals five days later. Equal amounts of rat liver S-9 prepared from the livers of treated animals were used in the Ames assay of the four mutagens. The investigators then compared the numbers of TA98 strain *Salmonella typhimurium* revertants induced by promutagens activated by the various S-9 mixes. S-9 mix from PenCB-treated rats was most active in producing benzo[a]pyrene-induced revertants. PenCB- S-9 preparations were also the most effective in producing Glu-P-1 and Trp-P-1 -induced revertants. As judged by the number of *Salmonella* revertants, phenobarbital S-9 preparations were most effective in activating AFB-1. HexCB was much less active than PenCB in activating benzo[a]pyrene, Glu-P-1, and Trp-P-1. The PCB congeners were similar in the amount of AFB-1 activated.

The studies finding a positive interaction (i.e., promotion) between PCBs and chemical carcinogenesis have been summarized in Table 3.7.14.

Table 3.7.14

Summary of Studies Reporting PCB Promotion of Chemical Carcinogenesis

Study	Carcinogen	Results
A. PCBs Administered After the Carcinogen :		
Nishizumi (1976)	diethylnitrosamine	promotion (liver tumors)
Kimura et al., (1976)	Me-DAB	promotion (liver tumors)
Ito et al., (1978)	N-2-fluorenylacetamide	promotion (liver tumors)
Preston et al., (1981)	diethylnitrosamine	promotion (liver tumors)
Pereira et al., (1982)	diethylnitrosamine	promotion (liver tumors)
Deml et al., (1983)	benzo(a)pyrene	promotion (liver tumors)
Arai et al., (1983)	dimethylnitrosamine	promotion (liver tumors) inhibition (kidney tumors)
Deml & Oesterle, (1987)	diethylnitrosamine	promotion (liver tumors) **threshold dose (1 mg/kg/day)**
Anderson et al., (1986)	dimethylnitrosamine	promotion ? (lung tumors) at a PCB dose of 500 mg/kg **NOEL ≤ 250 mg/kg (lung)** inhibition (liver tumors)
Mazue et al., (1983)	2-acetylaminofluorene	promotion (serum GGTase)
Buchmann et al., (1986)	diethylnitrosamine	promotion (liver lesions)

Table 3.7.14 (continued)

Summary of Studies Reporting PCB Promotion of Chemical Carcinogenesis

Study	Carcinogen	Results
Oesterle & Deml (1983)	nitrosamines	promotion (liver lesions)
Oesterle & Deml (1984)	diethylnitrosamine	promotion (liver lesions)
Greim et al., (1984, 1985)	diethylnitrosamine	promotion (liver lesions) No effect level (1 mg/kg)
B. PCBs Administered Before or with the Carcinogen:		
Shelton et al., (1984a)	dimethylnitrosamine	promotion (liver tumors)
Loury & Byard (1983)	trypophan, glutamate, pyrolysate	promotion of *in vitro* unscheduled DNA synthesis
Ozawa et al., (1985)	aflatoxin B-1, benzo(a)-pyrene, Glu-p-1, Trp-p-1	promotion of *in vitro* Ames test revertants

Me-DAB = 3'-methyl-4-dimethylaminoazobenzene
GGTase = gamma glutamyl transpeptidase

3.7.4.2 Studies Finding Either Antagonistic or Negative Interactions Between PCBs and Chemical Carcinogenesis

Anderson et al. (1983) examined the effect of PCBs on the carcinogenic action of N-nitrosodimethylamine (DMN) in Swiss mice. The authors injected pregnant Swiss mice with 500 mg/kg of Aroclor 1254 on day 19 of gestation. Suckling mice from the Aroclor 1254-treated mothers were then treated with intraperitoneal injection of 5 mg/kg DMN on postnatal day 4 or 14. Another group of suckling mice received injections of 100 μg DMN/kg on postnatal days 1, 4, 7, 10, 13, 16, 19, and 22. Mice from each treatment group were killed at age 28 weeks or 18 months and examined for liver and lung tumors. Mice treated with DMN on postnatal day four which were were born to mothers treated with Aroclor 1254 (Aroclor 1254 + DMN day 4) were significantly different from mice treated only with DMN in that the percentage of mice with liver tumors described by the authors as being "coalescing tumors" was approximately twice as high at 18 months. There were no other statistically significant differences between these groups with respect to the percentage of mice with liver or lung tumors or the numbers of liver or lung tumors per animal. In contrast, male mice treated with DMN on postnatal day 14 which were were born to mothers treated with Aroclor 1254 (Aroclor 1254 + DMN day 14) had significantly fewer lung tumors (33% vs 95%) and numbers of tumors per animal (1.3 vs 4.2) than mice treated with DMN alone. At 18 months, the lung tumor incidence in female mice treated with Aroclor 1254 + DMN on day 14 was 1.6 per animal whereas mice treated with DMN alone developed 7.6 lung tumors per animal. There were no significant differences in tumor incidence or average number of tumors per animal between mice treated with several small doses of DMN (which were born to mothers treated with PCBs) and mice treated with DMN alone. Thus, although Aroclor 1254 apparently enhanced liver tumor growth (as described by the incidence of mice with "coalescing tumors") in animals treated with DEN on day four, animals receiving DEN on day 14 were protected from its effects by PCBs. The authors suggested that PCB-induced enhancement of DMN demethylase, an enzyme responsible for DMN detoxification, was three-fold greater at day 14 than at day four, thus protecting mice treated with this procarcinogen on day 14.

In contrast to the results reported for liver carcinogens, PCBs do not promote skin carcinogens in the two-stage (initiation-promotion) system which uses mouse skin as the model (DiGiovanni et al., 1977; Berry et al., 1978; Berry et al., 1979). Using this test system Slaga and coworkers have tested PCBs for both initiation and promotion activity. They report that PCBs have little or no activity as initiators in the latter two studies (Berry et al., 1978; Berry et al., 1979), which contradicts the suggestion that PCB may be initiators as reported in their first study (DiGiovanni et al., 1977). The minimal change observed in the first study is probably attributable to the phorbol esters (TPA) administered as the promotor as the authors failed to control for the activity of TPA alone (Berry et al., 1978). In the latter two studies these investigators measured the promotional activity of both PCBs and TCDD. Neither PCBs or TCDD had any promotional activity when administered alone or following the administration of dimethylbenzanthracene (Berry et al., 1978; Berry et al., 1979). In fact, prior administration of PCBs and TCDD actually reduced the carcinogenicity of dimethylbenzanthracene (Berry et al., 1979).

Kerklivet and Kimeldorf (1977a) studied the effect of PCBs on the growth of transplantable tumors in Sprague-Dawley rats. Male rats were fed diets containing 5, 25, 100, 400, or 800 ppm Aroclor 1254. Female rats were fed 100, 400, or 800 ppm Aroclor 1254 in the diet. After 30 days of exposure to the Aroclor 1254-contaminated diets, the rats were injected in each hind limb with 1×10^5 Walker tumor cells and were continued on the contaminated diets for nine days. Tumor growth and incidence was examined on the ninth day. Aroclor 1254 significantly reduced tumor weight in male rats for all doses tested. At the 100 ppm dose, average tumor weight was 75% of control. Although tumor weights were even lower in rats fed 400 and 800 ppm Aroclor 1254, body weight gain was also significantly reduced. Weight gain in male rats was unaffected in groups fed 5, 25, and 100 ppm. Aroclor 1254 treatment also reduced average tumor weight in female rats, but this effect was accompanied by depressed body weight gain. Although reduced body weight gain may have caused decreased tumor growth in the high PCB exposure groups, this explanation does not account for the PCB-induced depression of tumor growth at low doses. This study confirmed the

results of other work by Kerklivet and Kimeldorf (1977b) which indicated that intraperitoneal injections of Aroclor 1254 (100 mg/kg every other day) decreased the number of tumors formed, tumor weights, and slightly increased tumor latency in a similar experimental model. Therefore, these studies suggest that PCBs (Aroclor 1254) may have significant antitumor activity at doses lower than those generally used in tumor promotion studies.

The initiating activity of Aroclor 1254, a mixture of PCB isomers found in human breast milk, which included 13 different PCBs (HBM-PCB), or three different PCB isomers, was investigated by Hayes et al. (1985). Suckling Fischer 344 rats were given one or three oral doses of 500 mg/kg Aroclor 1254 on postnatal days 2, 5, and 14, or 400 μmol/kg HBM-PCB or 400 μmol/kg of either 2,2',5,5'-tetrachlorobiphenyl, 2,2',4,4'-tetrachlorobiphenyl, or 2,2',4,4',6,6'-hexachlorobiphenyl on postnatal days 3, 10, or 17. Rats were given 2-acetylaminofluorene (2-AAF) for three consecutive days followed by partial hepatectomy to induce cell proliferation and thus select for gamma glutamyl transferase (GGTase) positive foci. The rats were killed and the livers examined three weeks later for GGTase positive foci. In a second experiment, adult Fischer 344 rats underwent partial hepatectomy followed by an oral dose of 500 mg/kg Aroclor 1254, 400 μmol/kg HBM-PCB, or 400 μmol of one of the three above-named PCB isomers two hours later. Four weeks later, rats were given 2-AAF and carbon tetrachloride to select for GGTase-positive foci and were killed three weeks later. No GGTase-positive foci were detected in any PCB-treated animals. In contrast, known initiators of carcinogenesis such as diethylnitrosamine, benzo[a]pyrene, or methylcholanthrene produced GGTase-positive foci. The authors concluded that the doses of various forms and isomers of PCBs tested had no initiating activity.

Makiura et al. (1974) studied the effect of Kanechlor 500 on the tumorigenic effects of 3'-methyl-4-dimethylamino-azobenzene (3'-Me-DAB), 2-acetylaminofluorene (2-AAF), and diethylnitrosamine (DEN) in male Sprague-Dawley rats. Rats were fed diets containing 0.03% 3'-Me-DAB or 0.015% 2-AAF or drinking water containing 0.0025% DEN and 0 or 0.05% Kanechlor 500

for 20 weeks. Animals were killed at 24 weeks and examined for liver changes. The incidences of hepatic nodular hyperplasia in animals fed 3'-Me-DAB, 2-AAF, and DEN were 95.7%, 100%, and 100%, respectively. The incidence of hepatic nodular hyperplasia in rats fed the same carcinogens with 0.05% Kanechlor 500 were 0%, 5.9%, and 0%, respectively. Hepatocellular carcinomas were observed only in rats fed 3'-Me-DAB, 2-AAF, and DEN without PCB. Thus, concurrent administration of PCB with 3'-Me-DAB, 2-AAF, and DEN protected against the tumorigenic effects of these hepatocarcinogens.

Nesnow et al. (1981) investigated the effect of Aroclor 1254 on the transformation of C3H10T1/2CL8 mouse embryo fibroblasts by benzo[a]pyrene. Cultured fibroblasts were treated for 48 hours with 0.3, 1.0, 3.0, 10.0, or 30 μM Aroclor 1254 and then with 4μM benzo[a]pyrene for 24 hours concurrently with Aroclor 1254. The cultures were then given fresh medium and allowed to grow to confluence. Fibroblasts were scored for transformed cultures after six weeks of culture. Aroclor 1254 (1.0 μM) produced only a marginal increase (40%) in cells transformed by benzo[a]pyrene. Other concentrations did not increase cell transformation. Aroclor 1254 treatment also reduced the amount of benzo[a]pyrene metabolites produced by the cultured fibroblasts. The authors did not consider Aroclor 1254 to be an agent capable of producing a stimulatory effect on benzo[a]pyrene-induced cell transformation.

Gans and Pintauro (1986) described an effect of Aroclor 1254 on the liver which had not been described previously. Male CD-1 mice were treated with 40 ppm diethylnitrosamine (DEN) for eight weeks, followed by a 2.5 week period with no treatment. The mice were then given intraperitoneal doses of Aroclor 1254 (100 mg/kg) every other week for 16 weeks. Animals were sacrificed and examined after DEN treatment, after four PCB doses, or after eight PCB doses. No significant difference was observed between mice treated with only DEN versus DEN + PCB with respect to the number of liver nodules induced per animal. Thus, PCBs did not have any promotional activity in this experiment. However, 15 of 18 animals treated with DEN + PCB had liver scarring that was different in character than that produced by either alcohol or carbon tetrachloride. This

scarring was also seen in one of 19 animals treated with DEN alone, but the significance of these fibrotic liver changes with respect to tumorigenesis is not known.

Nishizumi (1985) examined the effect of PCBs on dimethylhydrazine-induced colon tumorigenesis in the rat. Male Wistar rats were treated with subcutaneous injections of dimethylhydrazine (30 mg/kg) weekly for 10 weeks. Rats were given oral doses of Kanechlor 500 twice a week for three weeks either before or after the 10-week treatment with dimethylhydrazine (DMH). Animals were killed at 18, 24, and 28 weeks after the start of DMH treatment. There were no significant differences in the incidence of duodenal or colonic tumors between groups which were treated with DMH, DMH + PCBs (DMH before PCB), or PCBs + DMH (DMH after PCB treatment). At 28 weeks, the average number of duodenal and colon tumors per animal in PCB + DMH and DMH + PCB-treated animals appeared to be higher than in rats treated with DMH alone, but these differences were not statistically significant. Also, at 28 weeks, the average distance of colon tumors from the anorectal junction in the PCB + DMH treatment group was significantly larger than that observed for colon tumors in the DMH + PCB or DMH-only groups. In the DMH + PCBs and PCBs + DMH treatment groups, average colon tumor size at 28 weeks was significantly higher than the DMH-only group. The author suggested that this was sufficient evidence for concluding that PCBs have an enhancing effect on colon tumorigenesis induced by DMH. However, since there were no clear differences in the tumor incidences between treatment groups and the DMH control, this conclusion is not supported by the results.

Nishizumi (1980) fed female Wistar strain rats dosages of 200 mg/kg of Kanechlor-500 (group 1), 40 mg/kg Kanechlor-500 (group 2), and 0 mg/kg Kanechlor-500 (group 3) on days 5, 10, and 15 of gestation. At the age of 28 days, the offspring of each group were separated by sex and given 50 ppm diethylnitrosamine in drinking water for five weeks. Animals were sacrificed at 16, 20, and 24 weeks after the start of nitrosamine exposure, and their livers were examined. The number of small liver nodules (<5 mm in size) per male rat were 2 and 5.8 in group 1, 4.7 and 8.3 in group 2, and 6 and 13 in group 3, at 20 and 24

weeks, respectively. The average number of liver tumors per male rat of group 1 was significantly less ($p < 0.05$) than that in control group 3 at both 20 and 24 weeks. Similarly, the average number of liver tumors in group 2 for male rats was significantly less ($p < 0.05$) than that in control group 3 at 20 weeks. No liver tumor (>5 mm in size) was observed at 20 weeks in female rats of group 1, while one tumor per rat on average was observed in control group 3. There was a consistent decrease in the average number of liver tumors produced in groups 3, 2, and 1, in that order, for both males and females. Nishizumi reported that the tumor-inhibiting action of PCBs was more distinct in males than females, presumably due to the difference of sensitivity to PCB. He concluded, therefore, that a microsomal drug-metabolizing enzyme system may be involved in this tumor-inhibiting action induced by placental and mammary transfer of PCB.

Shelton et al. (1984b) demonstrated that PCB-exposed rainbow trout developed fewer aflatoxin B-1 (AFB-1)-induced liver tumors than fish exposed to AFB-1 alc. Trout were exposed to 1, 4, or 8 ppb AFB-1 and 0 or 50 ppm Aroclor 1254 in the diet. Other groups were fed 4 ppb AFB-1 + 5 ppm Aroclor 1254 or only 50 ppm Aroclor 1254. The incidence of hepatocarcinoma was examined after nine and 12 months of exposure. Trout fed 1, 4, or 8 ppb AFB-1 had tumor incidences of 3.8%, 9.8%, and 52% at nine months and 22.3%, 54%, and 83% at 12 months, respectively. Feeding of 50 ppm PCBs and 1, 4, or 8 ppb AFB-1 reduced tumor incidences in these groups to 0, 5.1%, and 20% at nine months and 11.7%, 31.2%, and 74.6% at 12 months, respectively. Trout fed only 50 ppm PCB developed 1.4% and 0% tumors after 9 and 12 months, respectively. In a separate experiment, *Salmonella* revertants produced by AFB-1 were reduced 35 to 65% when hepatic activation systems were prepared from livers of trout fed 50 ppm PCB for a year. The results of these studies suggest that PCBs protect against the carcinogenic and mutagenic effects of AFB-1 in trout by enhancing its metabolism.

Stott and Sinnhuber (1978) demonstrated that pretreatment of rainbow trout (*Salmo gairdneri*) with 500 mg/kg of body weight dosages of Aroclors 1242, 1254, and 1260 significantly reduced the mutagenicity of aflatoxin B_1 as measured by the Ames mutagen assay, compared to control. The effect produced by Aroclor 1221

was similar to that of controls. A pattern of decreasing response with increasing chlorination number was observed, except with Aroclor 1260. Interestingly, trout mixed-function oxidase activity is significantly increased by PCB pretreatment (Stott and Sinnhuber, 1978). Stott and Sinnhuber (1978) suggested that the apparent conflict between reported PCB induction of trout mixed-function oxidase system and of decreased mutagen assay responses in PCB-treated fish may be that mutagen detoxifying enzyme systems were induced to a greater extent than the aflatoxin B1 activating mixed-function oxidase system.

Hendricks et al. (1980) exposed rainbow trout embryos to water containing 0.5 ppm aflatoxin B-1 (AFB-1) for one hour, and thereafter to feed containing 100 ppm Aroclor 1254 for one year. Fish were sampled after nine and 12 months. PCB cotreatment produced a greater incidence of liver tumors than AFB-1 treatment alone at the nine month interval; however, there were no differences between these groups in the incidence of liver carcinomas at 12 months. There were also no significant differences between these groups with respect to tumor diameter or tumors/liver at nine or 12 months. The authors suggested that the difference in tumor incidence observed at nine months between AFB-1 and AFB-1 + Aroclor 1254-treated fish may be due to a sampling error. The failure to observe any significant differences between these groups at 12 months suggests that this may be the case, as does the later study by Shelton et al. (1984b). Thus, Aroclor 1254 appeared to have no enhancing effect on AFB-1-induced liver tumorigenesis in rainbow trout exposed to AFB-1 as embryos.

The effect of pre-exposing fish to six-week diets containing 100 ppm of Aroclor 1254 on diethylnitrosamine (DEN)-initiated liver tumors has also been studied (Fong et al, 1988). Like studies in mammals, exposing fish to PCBs before administering DEN did not increase the number of DEN-induced liver tumors in trout. PCB treatment also had no effect on the DNA adduct formation. In contrast to the results with PCBs, indole-3-carbinol inhibited DEN-induced DNA alkylation and liver tumor incidence while β-naphthoflavone increased both DNA alkylation and tumor formation.

The studies finding a negative interaction (i.e., antagonism) between PCBs and chemical carcinogenesis are summarized in Table 3.7.15.

Table 3.7.15

Summary of Studies Reporting PCB Antagonism or Negative Interaction with Chemical Carcinogenesis

Study	Carcinogen	Results
A. PCBs Administered After the Carcinogen:		
Hendricks et al., (1980)	aflatoxin B1	no effect
Gans & Pitauro, (1986)	diethylnitrosamine	liver scarring no effect (liver nodules)
B. PCBs Administered Before or With the Carcinogen:		
Makiura et al., (1974)	Me-DAB N-2-fluorenylacetamide diethylnitrosamine	fewer liver tumors fewer liver tumors fewer liver tumors
Kimura et al., (1976)	Me-DAB	fewer liver tumors

Table 3.7.15 (continued)

Summary of Studies Reporting PCB Antagonism or Negative Interaction with Chemical Carcinogenesis

Study	Carcinogen	Results
Hendricks et al., (1977)	aflatoxin B-1	fewer liver tumors
Nishizumi (1980)	diethylnitrosamine	fewer liver tumors
Anderson et al., (1983)	diethylnitrosamine	fewer liver & lung tumors
Shelton et al., (1984b)	aflatoxin B-1	fewer liver tumors
Fong et al., (1988)	diethylnitrosamine	no change in liver tumor incidence
Kerklivet & Kimeldorf (1977a)	tumor cell injection	lower tumor incidence
Berry et al., (1978; 1979)	dimethylbenzanthracene, TPA (phorbol acetate)	fewer skin tumors
Hayes et al., (1985)	2-acetylaminofluorine, carbon tetrachloride	no initiation of liver lesions
Nesnow, et al., (1981)	benzo-a-pyrene	little or no effect in fibroblast culture
Nishizumi (1985)	dimethylhydrazine	no effect on G.I. tumors
Stott & Sinnhuber (1978)	aflatoxin B-1	reduced mutagenicity in the Ames Assay

Me-DAB = 3'-methyl-4-dimethylaminoazobenzene

3.7.5 Summary of Carcinogenicity Studies in Animals

PCB commercial mixtures varying from 42% to 60% chlorine content have been examined for carcinogenicity in chronic rodent bioassays. Just as most other effects of PCBs are dependent upon chlorine content, the carcinogenicity also appears to be a function of the extent of chlorination, with positive results consistently demonstrated only for mixtures of 60% chlorine. Results are conflicting for 54% chlorine mixtures, and the data for 48% and 42% are all negative.

It is interesting to note that while 60% chlorine PCB mixtures produce an increase in liver carcinomas, the overall tumor load for animals subjected to lifetime exposure to PCBs is unchanged or diminished. The liver tumors appear late in the life of the animal, and the animal seems to suffer no ill effect from them -- the rats in these studies lived as long or longer than the control rats. Therefore while highly-chlorinated PCB mixtures may be classified as carcinogenic in animals, the nature of the neoplastic response somewhat attenuates the concern for the impact of this potential effect on human health.

Another issue related to PCBs and cancer is their interaction with known carcinogens. Studies indicate that PCBs may either increase or decrease the tumorigenesis of other compounds, depending on the temporal relationship of the exposures. In general, PCB administration after administration of a carcinogen increases the tumorigenic response, while PCB exposure prior to or concurrently with the carcinogen decreases its tumorigenesis. It appears that the promoting effect of PCBs to increase tumorigenesis occurs at doses in excess of environmental doses that humans would encounter.

4.0 HUMAN TOXICOLOGY OF PCBs

4.1 COMMON SOURCES OF ENVIRONMENTAL CONTAMINATION AND POTENTIAL ROUTES OF PCB EXPOSURE

4.1.1 Historical Use of PCBs

The commercial production of polychlorinated biphenyls (PCBs) began in 1929 in response to the electrical industry's need for flame resistant dielectric insulating fluids for use in capacitors and transformers. PCBs were useful in a number of industrial and domestic applications because of their unique functional characteristics, such as thermal stability, low water solubility and flame retardant properties. Although the primary need for PCBs was as insulating fluids in electrical capacitors and transformers, their use widened to include applications in heat transfer fluids, hydraulic fluids, vacuum pump and compressor fluids, lubricants, plasticizers, adhesives, paints, caulking compounds, carbonless paper systems and waxes. Estimated production and uses of various Aroclor PCB mixtures during the period of highest PCB production in the United States (1960-72) is provided in Table 4.1.1. This table shows that capacitor and transformer uses comprised more than 50% of the domestic PCB uses each year during this period.

The increasing awareness of organochlorine pesticide contamination in the environment (e.g. with DDT) was stimulated by environmentalists during the 1960s. This awareness eventually led to the discovery in the United States and elsewhere that PCBs had become widespread environmental contaminants by the late 1960s. In 1968, public concern over the possible health effects of PCBs increased following the "Yusho" incident in Japan. As a result of a Japanese industrial accident, about 1,000 people became ill from eating rice oil heavily contaminated with Japanese-produced PCBs (Kanechlors). Though it was later found that the Yusho symptoms were probably caused by polychlorinated dibenzofuran contaminants (see Appendix A), the incident sounded a cautionary signal which promoted legislative actions in many countries to limit the production and use of PCBs.

Table 4.1.1

PCB Production and Usage in the U.S. (Metric Tons)

	Year						
USE	1960	1962	1964	1966	1968	1970	1972
DOMESTIC USE BY CATEGORY							
Heat transfer	-	78	464	883	1,264	1,979	376
Hydraulics/ lubricants	1,262	1,957	2,187	2,129	2,883	3,701	-
Miscellaneous industrial	779	847	846	889	642	813	-
Transformer	3,960	3,992	3,998	4,455	5,792	6,914	12,828
Capacitor	8,483	7,691	9,770	14,442	14,775	13,354	-
Plasticizer applications	3,722	4,462	5,168	6,740	7,202	9,768	-
DOMESTIC USE BY PCB GRADE							
Aroclor 1221	52	70	298	264	68	738	85
Aroclor 1232	77	112	6	8	45	130	-
Aroclor 1242	9,098	10,327	11,785	19,778	22,427	24,294	364
Aroclor 1248	1,414	1,731	2,619	2,507	2,447	2,036	404
Aroclor 1254	3,044	3,162	3,740	3,517	4,445	6,210	1,747
Aroclor 1260	3,665	3,297	4,267	2,937	2,626	2,445	152
Aroclor 1262	163	276	223	384	360	512	-
Aroclor 1268	94	105	95	142	140	165	-
Aroclor 1016	-	-	-	-	-	-	10,451
Production	18,960	19,176	25,416	32,924	62,427	42,527	19,300
Domestic Sales	17,604	19,021	22,434	29,539	32,558	36,530	13,204
Export	-	-	2,048	3,426	5,615	6,825	3,194

Source: Peakall (1975)

Following reports of the Yusho PCB incident in Japan, the United States Food and Drug Administration (FDA) initiated a nationwide survey to investigate the extent to which PCBs contaminated the food chain indirectly. Indirect contamination was through PCB-contaminated animal feed, industrial and environmental sources, and the use of PCB-containing paper food-packaging materials. After the FDA found evidence of widespread food contamination, it established guidelines limiting the levels of PCBs in foods and food-packaging products containing unavoidable residues from environmental and industrial sources. The FDA concluded it would be in the interest of the public health to reduce PCB occurrence and human exposures by limiting the entrance of PCBs into the food chain and the allowable levels of PCBs levels in foods (Sawhney, 1986). In 1970, cautionary measures were also taken by the U.S. manufacturer of PCBs, including the limitation of PCB sales for uses only in sealed systems and additional cautionary measures ensuring their safe shipment to prevent further environmental contamination. Since 40% of the PCB applications before 1970 had been in "open system" uses such as in plasticizers, hydraulic fluids and lubricants, this action substantially decreased PCB production and usage in the United States. In 1972, the federal Interdepartmental Task Force on PCBs concluded *"Their continued use for transformers and capacitors in the near future is considered necessary because of the significantly increased risk of fire and explosion and the disruption of electrical service which result from a ban on PCB use."* In the meantime, considerable research efforts were expended in the development of suitable alternatives for PCBs in these critical applications.

By 1976, the electrical industry developed suitable alternatives for PCBs; silicone compounds were adapted for use in transformers and phthalate esters were used in capacitors as PCB substitutes. In light of these new developments, the Toxic Substances Control Act of 1976 specifically banned the manufacture of new PCBs and prohibited use of existing PCBs except in a *"totally enclosed"* manner or where specifically exempted. The United States manufacturers terminated the production and sales of PCB products by September, 1977, and the PCB "banning" legislation became effective in 1979.

In spite of these measures, the problem of eliminating environmental PCB

contamination is far from solved. The tremendous popularity of PCBs in previous years resulted in the production of some 1.4 billion pounds of various PCBs by 1977, most of which were still in use. Indeed, an estimated 750 million pounds of PCBs are still in use today; 20% (162 million pounds) are used by electrical utilities in existing capacitors and transformers. Of the PCBs no longer in use, an estimated 300 million pounds were placed in landfills, 150 million pounds were exported, 50 million pounds were destroyed, and another 150 million pounds were dispersed in other areas of the environment. Therefore, eliminating even the majority of existing PCBs from the environment in the United States would be an imposing task.

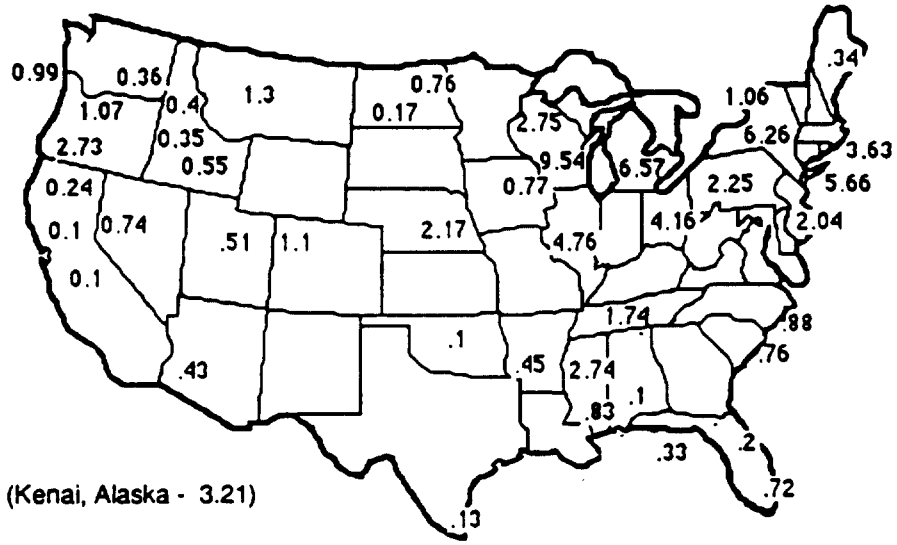
Finally, the PCB production in the United States represented only a fraction of the total world PCB production. NIOSH (1977) reported PCB production in France, Italy, the Soviet Union, Spain, Czechoslovakia, Poland, Argentina, Brazil, and India. In fact, PCBs are still produced in some of these countries. Therefore, the production, use, and environmental occurrence of PCBs will undoubtedly continue for many years to come.

4.1.2 Environmental Occurrence of PCBs

The extensive utilization of PCBs in industry created a specific geographical pattern of higher PCB concentrations in the more industrialized areas of the United States, as illustrated by the occurrence of PCBs in fish caught in various regions (Peakall, 1975; see Figure 4.1.1). Occasional spills or point sources of PCB contamination resulted in certain isolated areas of higher PCB occurrence in the environment. As a rule PCB occurrence coincides directly with highly industrialized and populated regions, particularly in the Northeast, Northwest, and Midwest (Great Lakes region) United States. Therefore, industrial PCB inputs into the environment in the past created a predictable pattern of PCB contamination in the United States.

Jensen (1966) was the first investigator of environmental PCB contamination in fish and wildlife, and his work created an interest in assessing the occurrence of PCBs in the global environment. Moore and Ramamoorthy (1984) studied the widespread occurrence of PCBs in the

PCB Content (ppm) of Fish in the U.S.



Source: Peakall, 1975

Figure 4.1.1

environment of not only the United States and Canada, but also England and Australia (see Table 4.1.2). Further evidence of the world-wide distribution of PCBs was provided by PCB measurements in Australian fur seals in southern Australia (Smillie and Waid, 1987), winter flounder from Long Island Sound (Greig and Sennefelder, 1987), blue crabs from a South Carolina estuary (Marcus and Mathews, 1987) and snapping turtles from the Upper Hudson River area (Byran et al., 1987; Olafsson et al., 1983). Remote high altitude lakes in the Rocky Mountain National Park were also noted to contain measurable PCB contamination in the sediments (Heit et al., 1984). The occurrence of PCBs in such pristine and unpopulated regions undoubtedly illustrate the movement of PCBs via atmospheric transport. As shall be discussed later, atmospheric transport of PCBs is thought to be a critical factor in their environmental disposition.

The National Pesticide Monitoring Program recently provided evidence of the historical and geographical pattern of PCB distribution in the United States that indicates the environmental concentrations of these persistent compounds are declining. Schmitt et al. (1985) published a summary of extensive sampling of region-specific organochlorine concentrations in freshwater fish tissu performed under the National Pesticide Monitoring Program. The authors noted, although DDT was still the most widespread organochlorine contaminant in the 1980-81 sampling period (found in fish at all monitoring stations), 94 % of the stations sampled also detected PCBs in fish tissue. Schmitt et al. (1985) also noted stations where fish PCB concentrations had been high in the past (in certain areas of the northeast, the Upper Mississippi River system, the Ohio River system, Cape Fear, N.C., and the Great Lakes) again reported the highest fish PCB concentrations, supporting their persistence in the aquatic environment. However, the authors also noted the reported maximal fish PCB concentration at each station has gradually decreased since 1976, and this trend was clear from the geometric mean of PCB concentrations (wet weight basis) from all samplings during the program testing periods (1976-77: 0.88 ppm; 1978-79: 0.85 ppm; 1980-81: 0.53 ppm). In fact, the most recent sampling represented a highly significant ($p \leq 0.01$) decrease in fish tissue PCB concentrations overall. Schmitt et al. (1985) concluded the concentrations of some of the most persistent organochlorine compounds were lower in 1980-81

Table 4.1.2

Concentration of PCBs in Marine and Fresh Waters

Location	Average (ng/l)	Range (ng/l)	Year
	Dissolved		
English Channel	0.19	0.15-0.30	1974
Irish Sea	0.50	<0.2-1.0	1974
Mediterranean Sea	2.0	<0.2-8.6	1975
Grand River (Canada)	5.8	ND-100	1975-76
Grand River (Canada)	3.7	ND-100	1976-77
Saugeen River (Canada)	0.20	ND-3	1975-76
Saugeen River (Canada)	0.30	ND-5	1976-77
	Suspended Solids (µg/kg)		
Inland waters (19 states, USA)	-	ND-4000	1971-72
Dority Reservoir (USA)	99	70-130	1978
Tiber Estuary (Mediterranean)	297 135	9-1000 ND-380	1976 1977
Baltic Sea	5.0	0.3-139	1977
Brisbane Estuary (Australia)	-	ND-50	-
Niagara River (Canada)	961	-	1979-80

ND = not detected
- = no data

Source: Moore and Ramamoorthy, (1984)

than at any time since the early 1970s, but residues of many persistent pesticides were still high enough in 1980-81 to constitute a threat to fish and wildlife.

There are three important sources of PCB contamination in the environment: 1) the intentional or unintentional discharge of PCB-contaminated effluent into public waste treatment plants or directly into the environment, 2) the disposal or storage of improperly contained liquid PCB wastes in landfills, pits or other locations, and 3) the incomplete burning of PCB-contaminated wastes by industrial, municipal, or even residential incineration. It is difficult to estimate what proportion of environmental PCB contamination can be attributed to each of these sources, because they are intertwined in their overall contribution to PCBs present in the environment.

Effluent discharge of PCB-contaminated water occurred for many years from both industrial and municipal sources. The previous usage of PCBs in plastics, lubricant oils, and heat transfer fluids provided a great potential for PCB contamination of effluents through intentional or inadvertent disposal of PCB wastes by individuals, small industry and government, as well as by large industry (Mowrer et al., 1977). Gaffney (1977) reported the formation of mono-, di-, and trichlorobiphenyls resulting from the final chlorination of municipal wastes containing biphenyl, and this is another potentially widespread source of PCBs. Once PCB effluent waters reach the municipal treatment facility or environmental waters, the low solubility of more heavily chlorinated congeners causes them to adsorb relatively tightly to organic particles. The low volatility of the mono-, di-, and tri- and chlorobiphenyls results in significant evaporation from the water and into the ambient air (Eisenreich et al., 1981b).

This characteristic movement of PCBs from water to air and sediment is an extremely important matter in the assessment of human PCB exposure through environmental pathways. The disposition of PCBs in water is not discussed in this report, but it is important to realize the solubility characteristics of PCBs allow only a negligible amount to actually become dissolved (usually in parts per trillion) (Swain, 1981; Eisenreich et al., 1981b) and thus sedimentation and volatilization pathways are generally more important in terms of the

environmental occurrence, transport and concentration of PCBs.

The past disposal of improperly contained or uncontained lubricants and industrial products such as PCB capacitors and transformers in landfills or open areas provided a second important source of PCBs in our environment (Dunphy and Hall, 1978a&b; NAS, 1979; Kimbrough, 1980). These items were previously disposed of in open, unlined pits or buried in landfills or quarries long before the possible hazards of PCBs were known. Today, we are only beginning to realize the extent of environmental contamination our past disposal practices caused and will continue to cause (WHO, 1976; IARC, 1978; NRC, 1979; D'Itri and Kamrin, 1983). The human exposure potential from PCBs dumped in landfills or open areas is highly dependent upon the nature of the site and the nature of the PCB and other contamination present. For example, Kimbrough (1980) observed that the spread of PCBs and other persistent chemicals becomes more likely when they are buried or discharged with organic solvents, which enhance their solubility and their ability to migrate into the environment. Detergents or emulsifiers can similarly increase PCB distribution from localized dump sites. However, even in the presence of solvents, detergents or emulsifiers, PCBs in soil usually do not spread to a significant extent and are rarely found in groundwater (Kurtz, 1978). The high affinity of PCBs for the soil results in only minimal migration and usually negligible transport of PCBs off-site. PCBs adsorbed onto dust or suspended particles may migrate if the site has not been properly contained. Of course, if the waste site is not isolated from potential human contact, dermal contact with soils may provide some degree of PCB exposure. As well, volatilization of the lower-chlorinated PCBs is also a source of contamination export from waste sites. Therefore, although the improper disposal of PCB wastes often does not result in the significant spread of PCB contamination, the improper containment of waste sites provides some potential for human exposure.

A third and probably most important source of PCB transport within the environment is through atmospheric pollution, originating from the incomplete incineration of PCB- or organochlorine-contaminated wastes or from the volatilization of lower-chlorinated congeners from various sources. Incineration of wastes is an extremely valuable method of disposal in many

instances. However, proper conditions (high temperatures) must be maintained to assure PCBs present in the waste are destroyed. Even if no PCBs are present in the waste, the incineration process can generate PCBs if chlorinated organic compounds are present and temperatures are too low. Industrial and muncipal incinerators burning organochlorine wastes undoubtedly were major contributors to atmospheric PCB pollution in the past. Permitting and monitoring processes instituted by local and federal government agencies now help to control this source, as is the case for industrial wastewater effluent PCB sources. The residential burning of contaminated heating oils and PCB-containing garbage are additional sources which individuals may inadvertently produce. Much of the PCB generated through incineration are likely to be adsorbed to dust or ash particles, but the atmospheric transport of these contaminated particulates certainly contributes to their wide distribution and concentration in the environment. Therefore, there exists a high potential for airborne PCB input and transport. The combination of wind and precipitation appear to allow the spread of PCBs everywhere in our environment.

Other sources of PCBs noted in the literature probably provide only minimal contributions to the background presence of PCBs in the environment. Plimmer and Kligebeil (1973) reported the irradiation of DDT by sunlight can produce PCBs. Similarly, sunlight may promote the formation of mono-, di-, tri-, tetra-, and hexachlorobenzenes in the environment (Uyeta et al., 1976).

4.1.3 The Atmospheric Transport of PCBs Through the Environment

Although the water column may be the largest sink for atmospheric deposition of PCBs (Eisenreich et al., 1981b), their characteristic low water solubility and high affinity for organic particulates predict sediments are the ultimate sink for PCBs and will continue to be a major source of contamination to the food chain for many years to come. Estimates of PCB flux to bottom sediments (440 kg/year) and volatilization from water (320 kg/year) in the Great Lakes suggest both volatilization and sedimentation are important PCB removal mechanisms from lakes (Swackhammer and Armstrong, 1986; Eisenreich et al., 1981b; Weininger and Armstrong, 1981). An important factor which may

contribute to sedimentation losses of PCBs is the reductive dechlorination of the higher-chlorinated PCB congeners by anaerobic bacteria present in bottom sediments. Brown et al., (1987) described the occurrence of distinct congener selection patterns in sediments from six PCB spill sites where slow shifts to less-chlorinated PCBs were observed. A recent study of Lake Superior demonstrated that when lake bottom sediments are disturbed, the water column PCB concentrations increase (50%), but the maximal PCB concentrations dissolved in water were always less than 2 parts per trillion (Baker et al., 1985). These authors also noted seasonal resuspension of sediments resulted in a cycling of PCB congeners dependent upon their degree of chlorination, with the heavier chlorinated congeners lost quite rapidly from the water column (half-time of 17-28 days). These findings again illustrate the predictable nature of environmental PCB deposition based upon their chemical properties, particularly their degree of chlorination and water solubility.

The deposition of PCBs into large bodies of water was the subject of many investigations, and some attempted to estimate the relative contributions of atmospheric PCB inputs. These input-output estimates must be highly complex and multi-factored because PCB deposition and cycling is highly dependent upon changes in meteorological conditions (winds, temperatures, precipitation). For this reason, total PCB burden of the lakes as well as surface area estimates of water surface and lake basin region must be modeled into the estimations (Eisenreich et al., 1981a&b; Weininger and Armstrong, 1981; Eisenreich and Johnson, 1983; Murphy and Rzeszutko, 1977; Swackhammer and Armstrong, 1986). There was general agreement among the estimates obtained for the Great Lakes region that the majority (60-90%) of lake PCB burdens are the result of atmospheric deposition (Moore and Ramamoorthy, 1984; Eisenreich et al., 1981b; Murphy and Rzeszutko, 1977). The National Academy of Sciences (NAS, 1979) reported their data indicated PCBs emitted in North America are ultimately transported in the atmosphere to the North Atlantic Ocean. Thus, the atmosphere transports PCBs. The ultimate PCB reservoirs are the sediments and waters of the Atlantic Ocean and the Great Lakes.

4.1.4 Levels of PCB Exposures From Outdoor Environments

The deposition of PCBs from air and water to soil was largely addressed above, but some additional points can be illustrated. Of an estimated 350,000 tons of PCBs released into the environment of North America by 1972, 85% was thought to be buried in landfills or dumps (Nisbet and Sarofim, 1972). In 1972, Carey and Gowan (1976) surveyed urban and rural area soils throughout the United States and found only 0.1% of the soil was contaminated with detectable levels of PCBs. They also determined 63% of these positives were from metropolitan areas, a finding probably related to industrial inputs of PCBs into the atmosphere. A similar soil study in Japan showed that 40% of soil samples were below 0.01 ppm; 24% had 0.01-0.1 ppm; 21% had 0.11-1.0 ppm; 7% had 1.1-10 ppm; 3% had 10.1-100 ppm and 5% had more than 100.1 ppm PCBs (Tatsukawa, 1976). Of course, such estimates of soil PCB distribution are highly dependent on the choice of sampling areas and may not reasonably represent the true degree of PCB contamination present.

The use of PCB-contaminated soils in crop production was also shown to be a relevant exposure pathway in the past. PCBs are taken up by a number of plant species and can be phytotoxic. Tatsukawa (1976) found PCB levels in unhulled rice grown in various regions of Japan ranging from < 0.01 ppm to 10 ppm, levels roughly correlating with the degree of soil contamination. Similarly, soil and crop contamination via PCB-containing sewage sludge used for fertilizer was reported by Bergh and Peoples (1977). Therefore, crop contamination via PCBs in the soil can be seen as a parallel process with fish contamination via PCBs in the sediment, and both processes have potential impact on human PCB exposure.

As indicated above, the actual air PCB concentrations are highly dependent upon the distance from potential input sources and meteorological conditions. Air monitoring reports from Japan noted differences in the air PCB concentrations from 2-5 ng/m^3 in rural areas to 20 ng/m^3 in urban areas and as much as 12,000 ng/m^3 near electrical appliance factories and paper recycling mills (Tatsukawa, 1976; Tatsukawa and Watanabe, 1972). In the United States, 1976 air PCB concentrations in rural areas reportedly averaged 100 ng/m^3 (Kutz

and Yang, 1976), but values below 20 ng/m^3 were reported recently for field blanks in an urban area (Oatman and Roy, 1986). In general, PCBs present in the outdoor air are likely to be rapidly diluted and are often much lower than air PCB concentrations found inside public buildings and homes (MacLeod, 1981; Oatman and Roy, 1986).

A recent report by Jan and Tratnik (1988) suggests under some circumstances the dermal route may be an important pathway for outdoor environmental exposures. Yugoslavs living along the Krupa river had PCB blood and fat levels considerably higher than levels in people living nearby but not on the river. Measurements of the environmental conditions associated with the river indicated PCB concentrations reached 0.3 ppb in water, 55 ppm in sediment, 117 ppm in fish, and 0.5 μg/m^3 in air. Apparently, the local residents laundered their clothes in the river, and clothing samples contained as much as 0.8 ppm of PCBs. Eighteen and 25 months after they ceased using the river for bathing and laundry purposes, there was a rapid decline in the PCB blood and fat concentrations of the residents. Based on this observation, the authors suggested dermal exposure was probably the predominant exposure pathway.

Several studies have attempted to correlate the consumption of locally contaminated fish with higher-than-normal PCB exposures. Under the sponsorship of the FDA, the Michigan Department of Public Health conducted a study of 182 adults consuming fish from the Great Lakes area, 105 of whom had ingested more than 26 pounds of fish each year (Humphrey, 1980). The PCB blood levels in these people correlated significantly with their level of fish consumption. The mean blood PCB concentration was 73 ppb for those who consumed more than 26 pounds of sport fish from Lake Michigan compared to only 20 ppb for individuals consuming six pounds or less, and 17 ppb for those who consumed no fish. A study has also been performed of residents of Triana, Alabama, an area of higher-than-normal PCB and DDT contamination (Kreiss et al., 1981). In 458 residents, the serum PCB levels ranged from 3 to 158 ppb, with a mean of 22.2 ppb. Ninety-eight of these subjects had serum levels in excess of 30 ppb, and 60% of these 98 persons had serum PCB levels exceeding 40 ppb; 40% of them were over 50 ppb.

In contrast to the two preceding studies, the Greater New Bedford PCB Health Effects Study (MDPH, 1987) found no correlation between fish consumptin and an elevation in blood levels of PCBs. In the late 1970s, PCBs were found in the New Bedford Harbor and the Acushnet River Estuary. Phase I of this health effects study was designed to determine the prevalence of elevated serum PCB levels in residents of Greater New Bedford. An elevated serum PCB level was defined as ≥30 ppb. Only 1.1% of the 840 participating residents of Greater New Bedford had elevated serum PCB levels. Consequently, an Enrichment Study involving individuals with presumed exposure to local seafood (and possibly sustaining greater PCB exposure) was undertaken in an attempt to identify a group with elevated serum PCB levels. Serum PCB levels of this group were, however, also within the typical range of the U. S. population. The majority of participants in the Enrichment Study reported eating locally trapped lobster five or more times in their lifetime, and some 25% reported eating locally-caught eel. Both species have been reported to contain very high PCB levels when taken from some parts of New Bedford Harbor. Therefore, the Greater New Bedford Health Effects Study suggests that an increased potential for environmental PCB exposure does not necessarily result in elevated PCB body burden.

Baker et al. (1980) examined residents and workers in Bloomington, Indiana, after it was discovered PCBs had been discharged into the municipal sewage system by a local capacitor manufacturing plant. Sewage sludge from this system was sold as fertilizer. Testing in August of 1976 had found significant PCB contamination in a number of places. The mean PCB concentrations were 479 ppm in sewage sludge, 17 ppm in treated soil, and 0.15 ppm in the vegetables grown in this soil. The mean serum PCB level was only 17.4 ppb in 89 persons listed in the study as sludge users. Interestingly, the mean serum PCB level in 22 community residents with no known exposure to PCBs was higher at 24.4 ppb.

Stehr-Green et al. (1986a) examined serum PCB levels obtained from people living near three different contaminated waste sites who were thought to be at high risk of PCB exposure. The authors found the high-risk-of-exposure group had average (geometric mean of the group) serum PCB levels of only 9 ppb. Most

members of this group had serum PCB levels that were less than 20 ppb (the normal range) with the exceptions being those people with previous occupational PCB exposure. In a pilot study of similar design Stehr et al. (1985) observed that, *"Whereas environmental contamination levels ranged from 2.5 µg/l in monitoring well samples, to 70 ppb in foodstuffs, to over 300,000 ppm in on-site soil in these situations, over 95% of the serum-PCB levels were within background ranges among those persons at highest risk of nonoccupational exposure."* Thus, these investigators concluded that while the levels of chemical contamination may be quite high at a waste site, actual exposure to and absorption of chemical contaminants may remain small or undetectable (Stehr-Green et al., 1986a).

The Agency for Toxic Substances and Disease Registry (ATSDR) conducted a detailed epidemiological investigation of the residents of Paoli, Pennsylvania, where widespread soil PCB contamination resulted through the long-term distribution of these substances from a highly contaminated rail yard (DHHS-ATSDR, 1987). Soil PCB concentrations up to 420,000 ppm were found in the contaminated rail yard where electric transformers were repaired and maintained. The PCB contamination in adjacent yards and street soils ranged up to 6,400 ppm, but this relatively high-level contamination was localized and soil PCB levels in the majority of residential yards were much lower (many less than 1 ppm). It was postulated that transport of contaminated soil and oil from the site during rainstorms resulted in the distribution of PCBs to nearby neighborhoods, as well as the elevated PCB levels in trout from local creeks. Therefore, an increased risk of resident PCB exposure seemed likely considering the environmental contamination present in Paoli.

The Paoli study design was largely based on the proposition that high levels of PCBs in residential soils should predict individual PCB body burden as indicated by serum PCB concentrations. ATSDR determined the serum PCB levels of 66 persons at highest risk of soil PCB exposure based on residential soil PCB levels, local topography, and proximity to the site. ATSDR compared the mean serum PCB concentrations in this "probability" group to a second "preselected" group of 23 residents with elevated residential soil PCB levels and to a third group, a cross sectional sampling of 396 persons thought to represent

the community in general. Contrary to expectations, the geometric mean and distribution of serum PCB concentrations in the Paoli cross sectional sampling did not differ from a large sample of people from across the United States with no known unusual source of PCB exposure. Moreover, the geometric mean serum PCB concentration of the "probability" group residents at high risk of soil PCB exposure did not differ from that of the cross sectional sampling. Perhaps even more surprising was the fact that the "preselected" group residents (i.e., residential soil PCB measurements exceeding 150 ppm) were not significantly different from the control population. In addition, the length of PCB exposure measured by the number of years of residence in the study area did not correlate with serum PCB levels, when the confounding influence of individual age was controlled. Individual age was the only variable which correlated significantly with the serum PCB level, as would be expected.

The conclusions reached by ATSDR have extreme importance concerning the potential risk of PCB exposure via contaminated residential soils. ATSDR concluded, *"The population in Paoli near the work site experienced exposure similar to populations found elsewhere in the United States showing typical background exposures. ... There is no evidence of increased exposure in the groups closest to the most highly contaminated soil."* So, even though clear evidence showed many of the residents were at potential risk of exposure to residential soils contaminated with PCBs (at concentrations vastly greater than that considered 'safe' by U. S. regulatory agencies), these soil PCB levels did not predict the actual body burden of people at high risk of exposure. Therefore, the Paoli Study, like those of Stehr-Green et al. (1986a) and Baker et al. (1980), indicates localized soil PCB contamination is not an important source of PCB exposure and soil PCB levels do not predict the PCB dose actually received by residents in the more heavily contaminated areas.

4.1.5 Levels of PCB Exposures From Indoor Environments

PCBs have been found in the pristine environments of the forest lands of Canada and the high altitude lake sediments in Rocky Mountain National Park, so it is not at all surprising our own environment is also contaminated with low

levels of PCBs in the air we breathe and the food we eat.

In the recent Drinking Water Health Criteria Document for PCBs, the USEPA (1987) judged the evidence of human exposure to PCBs from finished drinking water is limited. An earlier study under the National Organic Monitoring Survey (USEPA, 1977) determined of 113 cities monitored nationwide over an 11-month period, only 6% of the finished drinking water derived from groundwater sources contained quantifiable (0.1-0.2 µg/l) PCB concentrations. Similarly, finished drinking water derived from surface waters exhibited PCB concentrations above detection limits in only a few instances (1.1-3.3 % of samples per survey). Such observations probably result from the high efficiency (80-90 %) of PCB removal in the finishing process.

A number of studies attempted to measure and determine the source of air PCB contamination found inside public buildings. These studies demonstrated PCBs are present in the indoor air even when obvious sources of contamination are absent. Potential indoor sources of PCBs might include leaking fluorescent light ballasts, plastics, waxes, pesticides, inks, cutting oils, carbonless reproducing paper and photocopier toner mixtures (Schmitt et al., 1985; Hutzinger et al., 1974).

MacLeod (1981) measured indoor air PCB concentrations in laboratories, offices and homes and compared them to outdoor air PCB concentrations. The results of these investigations are provided in Table 4.1.3. These concentrations are quite low, and without long sample collection periods (days to months) PCB levels may not have been detectable. Based upon her findings, MacLeod (1981) concluded normal levels of PCBs found in indoor air are at least one order of magnitude higher than those in the surrounding outdoor atmosphere.

Another recent study examined the presence of PCBs in the air and on surfaces in public buildings (Oatman et al., 1985; Oatman and Roy, 1986) Schools, offices, and laboratories were used as sampling sites. Average airborne PCB levels ranged from 206-653 ng/m^3 in building with PCB transformers and from 117-327 ng/m^3 in buildings without PCB transformers

Table 4.1.3

Indoor Airborne PCB Levels

Site	#Samples	Average PCB Concentration (ng/m^3)
1. Industrial Research Facility		
Laboratory A	11	200
Laboratory B	6	240
Office A	2	110
Office B	2	80
Outdoor air	1	18
2. Academic Facility		
Laboratory	2	214
Outdoor air	2	4
3. Homes		
Kitchen A	1	480
Kitchen B	1	180
Kitchen C	2	250
Kitchen D	2	210
Kitchen E	3	240
Kitchen F	5	150
Kitchen G	2	580
Kitchen H	3	260
Kitchen I	5	500
Living room D	1	39
Bedroom E	3	70
Basement E	3	120
Library I	3	400
Outdoor air	1	4

Adapted from MacLeod (1981)

(Oatman and Roy, 1986). Average surface level PCB densities ranging from 0.1 - 0.8 $\mu g/100cm^2$ were measured in buildings with PCB-containing transformers, while 0.09 -0.37 μg PCBs/$100cm^2$ were found on surfaces of buildings without PCB-containing transformers (Oatman and Roy, 1986). The ability of PCBs on surfaces to be readily transferred to skin upon contact has been demonstrated (Christiansen et al., 1986).

Stark et al. (1986) examined 52 individuals (firemen, police, building personnel, and public utility employees) potentially exposed to PCBs while responding to a transformer malfunction. Apparently no fire occurred after the explosion, and polychlorinated dibenzofurans were not an issue in this incident. Fasting blood PCB levels were collected and compared to a control group of 68 "non-exposed" persons with similar occupations. The respective PCB blood levels for the exposed and nonexposed groups were 9.7-vs-7.1 ppb for the utility employees, 6.8-vs-7.4 ppb for the firemen, 6.6-vs-6.4 ppb for policemen, and 4.8-vs-5.9 for tenants. None of these differences were significant. Thus, no evidence of exposure was obtained in this study. This is perhaps not an unexpected finding as the reported PCB air concentrations in this building were only 0.3-1.7 $\mu g/m^3$; the ambient air quality standard for the State of New York is 1.7 $\mu g/m^3$.

Measurements of indoor air PCB concentrations of workplaces where PCBs are produced or used tend to dwarf the PCB levels found in homes, public buildings, and most laboratories. Occupational exposure to PCBs was estimated through air concentration measurements in many plant locations, particularly those plants which manufacture PCB-containing capacitors and transformers. In general, most occupational PCB exposure levels range from 0.1-1.0 mg/m^3 of air, but historically PCB levels ranging from 0.1-11.0 mg/m^3 were reported in various occupational studies (Jones and Alden, 1936; Meigs et al., 1954; Ouw et al., 1976; Fischbein et al., 1979; Brown, 1987; Nicholson et al., 1987). Comparing the historical occupational PCB concentration range to a common air PCB concentration found in homes and public buildings (200 ng/m^3), the magnitude of exposure in the workplace is some 500- to 55,000-fold higher.

In the early 1970s, the source of PCB exposure for most individuals in the

general population was probably from food and packaging materials. Kolbye (1972) reported of 3,505 samples of various foodstuffs examined by the Food and Drug Administration (FDA) in 1970 through 1971, about 1/6 were contaminated with PCBs at levels ranging from 0.25-2.27 ppm (Table 4.1.4). Based on the FDA estimates of the daily PCB intake for this period, the general population consumed several micrograms of PCBs each day (see Table 4.1.5). Continued surveillance indicated these levels declined for the years 1973-1975, perhaps as the result of better surveillance, the temporary tolerances established for that time, and the discontinued use of PCBs (Tables 4.1.6 & 4.1.7).

Other reports from this time period indicate similar or higher dietary ingestion rates in other parts of the world. For example, dietary intake of PCBs was estimated at between 4 and 50 µg/day in Japan (Tatsukawa, 1976) and 6-84 µg/day in home-prepared meals not containing fish in Switzerland (Zimmerli and Marek, 1973; as cited in Bennett, 1983).

Later reports confirmed declining levels of PCBs in food. Gartrell and colleagues at the Food and Drug Administration measured the levels of pesticides and industrial chemicals in infant and toddler diet samples for the years 1978 through 1982 (Gartrell et al., 1986a). Infant diet was found to contribute 0.011 µg PCBs/kg body weight/day in 1978, but had undetectable PCB levels in 1979-82. Similarly, toddler diet represented a dosage of 0.099 µg PCBs/kg body weight/day in 1978 but contained no measurable PCBs in 1979-82. Using PCBs measured in market basket samples, they also estimated PCB intake for adults from diet for these years, and calculated PCB dietary ingestion rates of 0.027, 0.014, 0.008, and 0.003 µg PCBs/kg/day for 1978, 1979, 1980, and 1981/82 respectively (Gartrell et al., 1986b). Assuming a body weight of 70 kg, this would correspond to an intake from diet of 0.21 µg/day for adults in the most recent years examined.

Table 4.1.4

PCBs in Selected Food Commodities (1970-1971)

Food	Number of samples examined	Number of samples positive (%)	Highest PCB levels (ppm)	Average (ppm)† PCB levels
Fish	670	363 (54)	35.29	1.87
Cheese	1344	91 (6)	1.0	0.25
Milk	941	69 (7)	27.8	2.27
Shell eggs	550	161 (29)	3.74	0.55
Fish by-product	-	13 (-)	5.0	1.17
Total (excluding fish by-product)	3505	684 (19)	-.--	1.14

Above results reflect both surveillance and compliance samples.
†Average residue levels do not include values indicated as "trace."
Source: Kolbye (1972)

Table 4.1.5

Estimates of Daily PCB Intake for the Teenage Male

Fiscal Year	Average Daily Intake of PCBs	
	Total Diet (μg/day)	Meat-fish-poultry Food Class (μg/day)
1971	15.0	9.5
1972	12.6	9.1
1973	13.1	8.7
1974	8.8	8.8
1975 (1st half)	8.7	8.7

Source: Jelinek and Corneliussen (1976); adapted from USEPA (1980)

Table 4.1.6

Summary of PCBs in Food
Fiscal Years 1973, 1974, and 1975

Food Commodity	1973 Percent Positive	1973 Max. (ppm)	1974 Percent Positive	1974 Max. (ppm)	1975 Percent Positive	1975 Max. (ppm)
Fish	60.4	123.0	44.0	16.8	17.8	9.0
Milk	2.2	1.6	2.6	2.3	0.7	1.9
Eggs	1.1	Trace	4.2	11.0	0.0	N.D.
Cheese	0.9	0.5	2.6	2.8	0.0	N.D.
Feed components	12.7	9.0	0.0	N.D.	0.3	0.9
Animal feeds	7.2	199.5	0.0	N.D.	0.0	N.D.
Processed fruits	4.5	19.2	0.0	N.D.	0.0	N.D.
Infant/junior foods	1.1	Trace	0.0	N.D.	0.0	N.D.

	Percent Positive	Percent above 5 ppm	Percent Positive	Percent above 5 ppm	Percent Positive	Percent above 5 ppm
Meats and poultry (USDA)	1.9	0.19	1.2	0.07	0.3	0.06

*Milk, cheese, meats and poultry reported as ppm, fat basis;
(Note: Detection limits - fish 0.5 ppm, other foods 0.05 ppm)
Source: Jelinek and Corneliussen (1976), adapted from USEPA (1980)

Table 4.1.7

FDA Regulations for PCBs

Commodity	PCB Concentrations	
	Temporary Tolerances (ppm)	Proposed Guidelines 1977 (ppm)
Milk (fat basis)	2.5	1.5
Dairy products (fat basis)	2.5	1.5
Poultry (fat basis)	5.0	3.0
Eggs	0.5	0.3
Finished animal feed	0.2	0.2
Animal feed components	2.0	2.0
Fish (edible portion)	5.0	2.0
Infant and junior foods	0.2	pending
Paper food-packaging material without a PCB-impermeable barrier	10.0	

Source: Jelinek and Corneliussen (1976; 42 FR 17487); adapted from USEPA (1980)
[Note: The temporary tolerance for fish was initially set at 5 ppm but later lowered to 2 ppm. For discussions of rationales for and against that change, the reader is referred to Cordle et al., 1982; Cordle, 1983; and Maxim and Harrington, 1984].

Matsumoto et al. (1987) performed the same market basket analysis for PCBs and pesticides in order to estimate daily intake from diet among Japanese in Osaka. The calculated PCB intakes were much higher than those reported by Gartrell and colleagues in the U.S. daily dietary intake of PCBs was reported as indicated below:

	Year						
	77	78	79	80	81	82	85
PCBs (μg/day)	3.3	3.2	1.5	2.2	1.1	1.4	4.3

(Note: The authors had no comment on the unusual increase in 1985 after a declining trend in previous years.)

Although most investigations did not focus upon human exposure to PCBs through sources other than our food supply and indoor air, it is evident low-level daily PCB exposure occurs through a variety of indoor activities related to business or leisure. Particularly, recycled paper products were noted to contain measurable PCB levels (Storr-Hansen and Rastogi, 1988), therefore reading a book or newspaper could result in low-level PCB exposure. Although there are contamination limits set by the FDA, paper and plastic materials in which food is packaged can contain measurable PCBs. PCBs may be present in used motor oils, so the home mechanic may sustain exposure in this way. In the office, inks, toner mixtures for photocopiers, and incidental exposure may also occur through contact with many household products or other items in common use. This includes powdered soap and toilet tissue (Williams and Benoid, 1979), recycled paper (Storr-Hansen and Rastogi, 1988), and non-carbon copy paper (although PCB use in this kind of paper has been discontinued) (Kuratsune and Matsuda, 1972). Plasticizers used in producing furniture, flooring and appliances may also contain PCBs and could contribute to daily indoor exposures, although the manner in which these products are used and their PCB contents suggests exposure from these sources is relatively minor. The wide variety of indoor PCB sources essentially precludes the possibility any person in our society will not be consistently exposed to PCBs at low levels.

Last, Fischbein and Wolf (1987) suggested family members of occupationally-exposed workers may have additional exposure through contaminated clothing. Two cases reported serum and adipose tissue PCB levels in PCB-exposed workers and their wives. The workers had elevated serum and adipose tissue PCB levels, and the PCB pattern resembled that of Aroclor 1254. The wives had serum and adipose tissue levels within the range of the general U.S. population, but the PCB pattern resembled that of Aroclor 1254. For non-industrially exposed persons, the PCB pattern generally resembles Aroclor 1260. Based on this difference alone, it was concluded the presence of an Aroclor 1254 pattern in the wives was indicative of exposure through PCB-contaminated clothing. PCB levels in the wives were not elevated, however, by this potential exposure route, and no clinical abnormalities were observed in these women.

4.1.6 PCB Environmental Occurrence and Exposure Summary

The same characteristics which made PCBs extremely useful in a variety of industrial applications resulted in their omnipresence in the environment upon disposal. Their high stability, low volatility and low water solubility lead to PCB concentration and persistence in the environment, two traits which led to the "banning" of PCBs and other organochlorines like DDT. PCBs are cycled between soil, air, water and biota and, although present at very low concentrations for the most part, they can bioaccumulate in higher species through food webs and may eventually lead to human PCB exposure.

Atmospheric movement of PCBs appears to be the most important PCB transport mechanism of distribution within our environment. Precipitation and atmospheric particle deposition provide a common path for PCBs to surface waters, eventually leading to their concentration and further biological cycling (resuspension or degradation) in bottom sediments. Lower-chlorinated PCB congeners appear to be driven from water to air through volatilization, and higher-chlorinated congeners remain in the sediment or are degraded to lower-chlorinated PCBs. Environmental losses of PCBs through sedimentation or the distribution/dilution of concentrated areas of contamination combined with microbial degradation of the more toxic, higher-chlorinated congeners may eventually solve a number of PCB contamination problems in our environment.

Government regulations restricting the use of PCBs and controlling their input into waters, municipal landfills, and the atmosphere undoubtedly contributed to the apparent decline in the PCB levels found in our environment and in our diets. Although the air PCB levels found inside our homes and businesses are often an order of magnitude higher than that found outside, both concentrations involve negligible exposure in comparison to the 500- to 55,000-fold higher PCB levels found in the air of some industrial workplaces. We are constantly reminded by further investigations that the many small sources of PCB exposure present both indoors and outdoors provide a low but consistent level of PCB exposure for everyone living in the U.S. or any other industrial nation.

Several studies sought to measure PCB tissue levels in persons exposed to PCBs from specific environmental sources. In none of these studies was actual exposure to PCBs found to exceed the exposure in the occupational setting, and in many studies the PCB body burdens of the participants in these studies were no different from those of the general, nonexposed population (e.g., MDPH, 1987; DHHS-ATSDR, 1987). Studies such as these demonstrate the need to evaluate carefully whether postulated exposure pathways are complete when attempting to identify populations at risk of exposure to PCBs or other persistent compounds found in the environment.

4.2 HUMAN PCB TISSUE LEVELS AND ESTIMATED TISSUE ELIMINATION RATES

4.2.1 Blood and Fat Tissue Levels

As stated in Section 4.1, PCBs were first recognized as an environmental contaminant in 1966. The magnitude of their environmental dispersal was quickly recognized during the next few years as scientists worldwide began to identify PCBs in the tissues of wildlife in Sweden, North America, Great Britain, the Netherlands, and even the Arctic (USEPA, 1980). It soon became obvious most persons in the United States and other countries were exposed to PCBs. As a result, it was predicted the tissue of most people would contain small amounts of PCB residues, particularly adipose tissue. This original assumption was later confirmed upon analysis of blood, adipose tissue, breast milk, and other human tissue and body-fluid samples.

The results of studies measuring PCBs in various tissues were widely reported. As will be apparent in discussion of the results of many of these studies, there is often significant variability in observed PCB levels. While some of this variability can be attributed to differences in exposure and in biological disposition of PCBs (distribution, elimination, etc.) among different populations, some variability may also arise from analytical methodology. Lawton et al. (1985b) recently reported random errors and interlaboratory variations in analytical procedures and methods of data reporting can have substantial impact on apparent PCB levels. For example, the 95% prediction interval for a single measurement of serum "Aroclor" was found to be ± 42%. Clearly, attention should be given to the methods of analysis and reporting when comparing exposure estimates or health effects studies from different laboratories. When methods are clearly described and assay approaches validated, such as through the process described by McKinney et al. (1984), there can be more confidence in the accuracy of reported values.

Since PCBs are lipophilic in nature, they tend to accumulate in adipose tissue. Therefore, PCB adipose tissue concentrations are generally considered to reflect the extent of exposure encountered by a person. Most studies

examining the PCB body burden in the general population use adipose tissue concentrations to make such determinations. Initially, the estimates of PCB body burdens in humans based on adipose tissue concentrations were, compared to later estimates, relatively high. Biros et al. (1970) found PCB concentrations of 200 and 600 ppm in two adipose tissue samples of unspecified origin. However, this initial observation was not supported in more recent investigations examining PCB body burdens in the general population. Price and Welch (1972) analyzed 196 fat samples from the general population and reported that while only 2.0% had no measurable levels of PCBs, 55.6% contained trace (<1.0 ppm) amounts, 36.7% had PCB concentrations of 1-2 ppm, and 5.6% had fat levels of PCBs exceeding 2.0 ppm. Yobs (1972) also analyzed fat tissue from individuals in the general population as part of the Human Monitoring Program. Based on 637 samples analyzed, he reported the following distribution: 34.2% had PCB levels that were below detection limits; 33.3% had trace (1.0 ppm) levels of PCBs, 27.3% had PCB concentrations between 1-2 ppm, and 5.2% had PCB levels in adipose tissue exceeding 2 ppm. In a follow-up of this study, Kutz and Strassman (1976) suggested environmentally-related exposures had increased between the early to mid-1970's. The percentage of persons with non-detectable PCB fat levels decreased from 34% to only 9%, the number containing less than 1 ppm increased from 33.35% to 50.6%, and the number of persons with PCB adipose concentrations between 1-2 ppm increased from 27.3% to 35.4%. This trend was confirmed in the report of Lucas (1982) who followed adipose tissue PCB residues in the United States population from 1972 to 1981. The Lucas investigation found the percentage of individuals with undetectable adipose PCB levels decreased through the observation period to 0% in 1981. This decrease was accompanied by a corresponding increase in the percentage of individuals with PCB levels up to 3 ppm. The percent of individuals with greater than 3 ppm reached a peak in 1977 (10%), and decreased steadily to become 1% by 1981.

There have been a few reports indicating the adipose PCB levels in individuals in specific regions of the United States. Burns (1974) measured PCB levels in 221 samples of adipose tissue removed during elective surgery from residents of the lower Rio Grande Valley in Texas. No PCBs were found among 26 samples in 1969 or 68 samples in 1970. In 1971, 15% of 88 samples were

positive for PCBs, with a mean PCB level of 1.7 ppm. Interestingly, in the following year no PCBs were found in 39 surgical adipose samples. A more recent study of PCB levels in residents of northeastern Louisiana found adipose PCB levels averaging 1.04 ppm in 1980 and 1.23 ppm in 1984 (Holt et al., 1986). These results were generally consistent with the national averages.

Studies of PCB fat levels in other countries revealed human levels in other parts of the world were approximately the same as, or slightly higher than, levels in the United States. Grant et al. (1976) and Mes et al. (1982) reported the PCB concentration in adipose tissue of the majority of Canadians averaged between 1-2 ppm, similar to that of the United States. In 1976, similar values (approx. 2 ppm) were reported for individuals in Finland (Hattula et al., 1976), though a later study found much lower values (Mussalo-Rauhamaa et al., 1984). In Germany, Australia, and Japan, mean PCB adipose-tissue concentrations higher than those discussed above have been reported. The mean PCB concentration in fat in the general populations of the Federal Republic of Germany, Australia, and Japan were reported as 6.8-10 ppm, 3.5 ppm, and 7.5 ppm, respectively (IARC, 1978; Tatesukawa, 1976a; 1976b). In Japan, as in the United States, the observed trend has been to lower PCB adipose levels in more recent years, with average adipose tissues concentrations of 5.43, 4.17, and 3.02 ppm measured in 1973, 1976, and 1981 (Mori et al., 1983). Watanabe et al. (1980) found average adipose tissue PCB levels to be 1.52 ppm among Japanese adults, and Kannan and coworkers, in a 1988 report, found average total adipose PCB levels in Japanese of approximately 1 ppm (Kannan et al., 1988).

The concentrations of PCBs in blood are generally two to three orders of magnitude less than those found in adipose tissue. While adipose tissue concentrations are usually reported in parts-per-million (ppm), blood concentrations are in the range of low parts-per-billion (ppb). Sahl et al. (1985) determined blood PCB concentrations in 738 employees of the Southern California Edison Company. The samples were derived as part of a pre-employment physical and were assumed to reflect blood PCB concentrations in the general population in the southern California area. The median blood PCB concentration was 4 ppb, within a range of 1 to 37 ppb. Interestingly, there were no blood samples with undetectable levels of PCB. Wolff et al. (1982b)

reported mean blood (serum) PCB concentrations of 4 ppb in children and 21 ppb (around Muskegon) and 9 ppb (rest of the state) for adults living in Michigan. Table 4.2.1 lists values determined in studies which have examined blood PCB levels in the general United States population.

Table 4.2.1

Background Blood or Plasma PCB Concentrations in the General Population of the United States[a,b]

Investigators	Number of observations	Mean value	Maximum value	Minimum value
Finklea et al., 1972	616	2.1	29.0	nd[c]
Humphrey et al., 1976	16	17.0	42.0	7.0
Baker et al., 1980	110	18.8	79.0	6.0
Drotman et al., 1981	17	7.5	30.0	2.0
Kreiss et al., 1982	1631	7.7	57.0	nd
Chase et al., 1982	19	12.0	27.0	nd
Condon, 1983	990	4.9	30.0	2.0
Emmett et al., 1983	54	4.5	15.0	nd
Humphrey, 1983	418	6.6	60.0	< 3.0
Reid and Fox, 1983	138	3.6	43.0	< 3.0
Welty, 1983	59	5.8	45.0	1.0
Welty, 1983	40	6.7	23.0	1.0
Sahl et al., 1985	738	4.0	37.0	<1.0

[a] All values in µg/l (ppb)
[b] Adapted from: Sahl et al.(1985); ATSDR (1987)
[c] nd = None detected.

4.2.2 PCBs in Breastmilk

One area of great concern is PCB exposure via human breast milk contamination and its uncertain impact on infant health (Kendrick, 1980; Wickizer et al., 1981). However, no human studies exist to suggest an unsafe human milk level of PCBs (Kendrick, 1980). The ability of PCBs to be passed from mother to nursing infant has been demonstrated in a number of studies (Kodama and Ota, 1980; Yakushiji et al., 1984; Ando et al., 1985). Kodama and Ota (1980) demonstrated, assuming that the cord blood PCB level was representative of the newborn infant's PCB blood levels at birth, that the PCB levels in the blood of breast-fed infants rose markedly with ingestion of human milk. Infant blood PCB levels exceeded those of their mothers at three months postpartum, and tended to increase until one year of age. These levels then gradually decreased at two and three years of age. However, the PCB levels in the blood of bottle-fed infants remained at a low concentration level during the same period. They concluded the quantity of PCBs transferred to infants from their mothers via lactation was much greater than that transferred placentally.

The concentrations of PCBs in breast milk are, therefore, of importance in assessing the potential for significant infant exposure. Savage and colleagues found PCBs in 20% of breastmilk samples from women in Colorado taken in 1971-72, with PCB levels ranging from 40-1000 ppb (Savage et al., 1973a&b). Savage (1977) later reported the results of a national study completed in the mid-1970's showing that out of 1,033 breast milk samples collected in the United States, 69% contained detectable levels of PCB, and 30% had values ranging from 50-4091 ppb (on a whole milk basis) with a mean value of 87 ppb. Wickizer et al. (1981) completed a more recent study confined to mothers in the state of Michigan, where, because of the contamination of the Great Lakes region, PCB body burdens probably run higher than the national average. Based on 1,057 samples ranging from trace levels of contamination to 5.1 ppm (on a fat weight basis), the mean PCB breast milk concentration was 1.5 ppm. They predicted based on this level, a nursing infant weighing 20 lbs would have a total PCB body content of 0.89 ppm by eight months of life, more than one-half of the PCB concentration in its mother's milk (Wickizer et al., 1981). Rogan et al. (1986a) reported a breast milk PCB concentration at birth of 1.8 ppm among 733 women

in North Carolina. In contrast, pooled samples from a national breast milk survey in 1982 showed 15.3 ppb (whole milk basis) and 397 ppb (milk fat basis)(Mes and Marchand, 1987). Other studies of human breast milk from women in other regions of the United States also found much lower concentrations (Bush et al., 1985; Slorach and Vaz, 1985) compared to the findings of Rogan et al. (1986a) and Wickizer et al. (1981).

The presence of PCBs and organochlorine pesticides was detected in human breast milk in other countries as well and is illustrated in Table 4.2.2. A recent study of Norwegian mothers (Skaare et al., 1988) found detectable PCB levels in milk from 80% (135/168) of mothers giving birth in Oslo, and updated the normal PCB milk content reported previously (Skaare, 1981) to a higher range (20-23 ppb whole milk basis). In a number of other countries the percentage of samples with detectable levels of PCBs was nearly 100 percent.

Mes et al. (1984) analyzed blood and breast milk samples from sixteen women over a 98-day lactation period. PCB concentrations in both maternal blood and breast milk remained relatively constant over this interval. PCB levels in breastmilk may vary during the day, however (Mes and Davies, 1978). Rogan et al. (1986a) measured PCB levels in breast milk of 868 women and attempted to identify factors associated with PCB levels. Breast milk measurements were made over 18 months, and PCB concentrations appeared to decline during this time. Women appeared to have higher levels during their first lactation. Levels declined with both time spent breast feeding and with number of children nursed. Higher levels were found in women who regularly drank alcohol, older women, and primiparae. This study indicates that there are a number of variables within a population that can influence the concentrations of PCBs in breast milk.

4.2.3 Estimated Tissue Elimination Rates

The level of PCBs in human tissue may decline over time. While there have been no rigorous studies of PCB pharmacokinetics in man, the data from a number of studies can be used to provide an approximation of the human rate of elimination of PCBs.

Table 4.2.2

Polychlorinated Biphenyl Concentrations in Breast Milk of Women in Countries Other Than the United States

Country	Basis	
	Whole Milk	Milk Fat
Canada	12-29 ppb	.085 - .0837 ppb
India/Pakistan	< 1 ppb	
Norway	2.1 ppb	126 ppb
Sweden		0.97 ppb
Finland	16 ppb	0.45 ppb
Denmark		0.81 ppb
Spain	0.25 ppb	
Japan	23-510 ppb	1.1-1.2 ppm

Adapted from Weisenberg et al. (1985), Slorach and Vaz (1985), Yakushiji et al. (1977), Currie et al. (1979), Mes and Davies (1979), Watanabe et al. (1980), Dillon et al. (1981), Skaare et al. (1988), Skaare (1981), Baluja et al. (1982), Wickstrom et al. (1983), Andersen and Orbaek (1984), Slorach and Vaz (1985).

Chen et al. (1982) measured the levels of a number of PCB congeners in the blood of 17 patients poisoned with contaminated rice oil in Taiwan. Two or three blood samples were measured over an approximate 12-15 month interval for each patient. Blood total PCB concentrations averaged approximately 46 ppb in the first sample, which was taken about 9 months after the ingestion of contaminated oil. Half-lives for two specific congeners, 2,4,5,3',4'-pentachlorobiphenyl and 2,3,4,3',4'-pentachlorobiphenyl, were estimated for each of the 17 patients. The half-life of 2,4,5,3',4'-pentachlorobiphenyl was calculated to be 9.8 $\pm$ 5.0 months (mean $\pm$ SD), while the half-life of 2,3,4,3',4'-pentachlorobiphenyl was calculated to be 6.7 $\pm$ 2.5 months. There were substantial apparent differences in elimination rates for the other congeners measured, though half-lives could not be estimated because they were either too long, too short, or the concentrations of PCB congener were too small to quantitate accurately. The relative rates of elimination of the PCB congeners were

consistent with principles of PCB metabolism established in detailed animal experiments, viz. the more highly-chlorinated congeners (hexa- and heptachlorobiphenyls) were eliminated more slowly, and isomers with *meta-para* unsubstitution were eliminated more rapidly than those with *ortho-meta* unsubstitution.

Yakushiji et al. (1984) measured total PCB blood levels in women occupationally exposed to Kanechlor 300 and Kanechlor 500. The PCB exposure period ranged from 7 to 19 years, and PCB use was discontinued three years prior to the first blood sample in 1975. Blood PCB levels measured in 1975 ranged from 8.3 to 84.5 ppb (mean, 39.0 ppb, N=13). In some of the women, blood samples were available for analysis in the subsequent 1-4 years (the last samples were in 1979). Using data from eight of these women, and assuming a monoexponential decline in blood concentrations, a half-life of 7.1 $\pm$ 2.7 years (mean $\pm$ SD) was calculated. Infants from many of these women were breast fed and consequently exposed to PCBs from breast milk. Blood samples from these children indicated an apparent rate of decline of PCBs in blood with a half-life of 2.8 $\pm$ 1.1 years. The authors concluded the shorter half-life in children was a consequence of a substantial dilutional effect from their growth. When the data were corrected for body weight gain, an excretion rate similar to the adult women (approximately 10% per year) was calculated for the children.

Steele et al. (1986), in a letter to the editor in the New England Medical Journal, presented estimations of PCB half-lives based upon PCB measurements in individuals with both occupational and non-occupational PCB exposure. The results from two blood samples were available for each individual in the study, one taken in 1977 and one from 1984. For those with occupational exposure (electrical equipment manufacture workers) PCB concentrations were expressed for lesser chlorinated PCBs (corresponding to Aroclor 1242), higher chlorinated PCBs (corresponding to Aroclor 1260), and total PCBs. Total PCB concentrations only were presented for those exposed to PCB-contaminated sludge (non-occupational exposure). Among those who had been exposed to PCBs occupationally, total serum PCBs ranged from 65 to 366 ppb in 1977 and from 15 to 75 ppb in 1984. The estimated half-life of lesser chlorinated PCBs in these individuals was 6-7 months, and the estimated half-life of the higher

chlorinated PCBs was 33-34 months. The overall rate of elimination of PCBs more closely resembled the results for lesser chlorinated PCBs. Serum PCB levels in the non-occupational exposure group generally ranged from 10 to 32 ppb in 1977, with one higher value at 116 ppb. In 1984, the serum PCB levels for this group were all similar to background levels in the U.S. population, ranging from 4 to 34 ppb. No estimate of half-life was presented for the non-occupationally exposed group. The estimations of half-life in this study were based upon the assumption of monoexponential decline of serum PCB levels throughout the 1977 to 1984 period. This could not be verified since only samples at two time points per individual were available for analysis. This may be a serious limitation, since 4/5 of the serum PCB concentrations from 1984 used in the analysis were essentially at background levels (15-39 ppb). To accurately estimate elimination half-life, it is also important that there be no further exposure to PCBs during the 1977 to 1984 interval. This is unlikely, and the persistence of lesser chlorinated PCBs, especially in the low-level exposure group (non-occupational), suggests continuing intake of PCBs.

There was a similar two-point estimation of PCB elimination rates conducted by Lawton et al. (1985), as part of a larger study of biochemical and hematological effects of PCBs among workers occupationally exposed. In the 29-month interval between samples, average body burden of lesser-chlorinated PCBs (i.e., up to and including some pentachlorobiphenyls) declined from 2.0 g to 0.4 g. Assuming a monoexponential decline in PCBs, this corresponds to a half-life of approximately one year. Similar calculations for higher-chlorinated PCBs were not feasible. A number of factors limit the accuracy of this estimation. These include a slight change in composition of the study group between the two sampling times, the required use of a correction factor for some of the analytical results, the use of concentrations from only two time points, and continued exposure to PCBs (Aroclor 1016) during a portion of the interval between samples.

A recent study examined the changes in blood and fat PCB levels with time following cessation of exposure to PCBs from an environmental source. Jan and Tratnik (1988) studied residents near the Krupa River in Yugoslavia which contains PCBs in the sediment, water, and fish. As part of this study, PCB blood

concentrations were measured in four residents who used the river for bathing and washing, and again 18 and 25 months after they stopped using river water. The changes in blood concentrations are indicated below.

Fat samples were also available for two of the subjects. In the 39-year old male subject, fat levels were 270 ppm in 1984 and 11 ppm 25 months later. The 50-year old male subject had fat levels of 320 ppm while using river water and 12 ppm 25 months after his use of river water stopped. Based upon the blood data for the four subjects, the half-life for PCB elimination would be appear to be

Table 4.2.3

Declining PCB Concentrations in Persons Environmentally Exposed to PCBs

age of subject	sex	PCB concentrations (ppb)		
		1984	18 mo. after cessation	25 mo. after cessation
10	male	41	15	9
34	female	135	46	
39	male	220	35	24
50	male	480	50	13

Adapted from Jan and Trantnik (1988)

approximately 6-8 months. The elimination rate from the fat, based upon these limited data, would have a shorter half-life. These half-life values may represent overestimations, as continued exposure to PCBs may have occurred (e.g. through inhalation of outdoor air near the river) during the 25-month period when river water was not used for washing or bathing. On the other hand, the estimates of PCB half-life from this study may be more realistic in that the blood PCB concentrations at the beginning of the study were sufficiently high that the confounding effects of background PCB exposure are minimized.

4.2.4 Summary of Environmental Exposure to PCBs

PCBs are ubiquitous in the environment. It is apparent from section 4.1 during the 1970's food was a major source of PCB exposure for the general population. Exposure from this source has probably diminished as a result of decreased introduction of PCBs into the environment and increased awareness and regulatory activity. More recent studies indicate that the general population continues to be exposed to PCBs from ambient air, with higher exposure from indoor air than outdoor air, and surface contamination in buildings. As a consequence of these exposures, virtually everyone in the U.S. still has measurable levels of PCBs in their blood and adipose tissue. Typically, serum PCB concentrations are in the low ppb range, while adipose tissue concentrations are roughly 1 ppm. This is not unique to the U.S., and individuals in other countries appear to have similar or higher body burdens. Measurable levels of PCBs are commonly found in breast milk, and this may be a source of PCB exposure for the breast-fed infant. If an unusual PCB exposure results in body burdens above background levels, PCBs are cleared from the body and tissue levels will return to background with time. The rate at which tissue levels decline appears to be congener dependent and influenced by the extent and position of chlorination. While the reported half-life for PCBs varies among the studies, an overall half-life (for total PCBs) of approximately six months was the most consistently reported value.

4.3 REPRODUCTIVE AND DEVELOPMENTAL STUDIES

4.3.1 Introduction

A number of published studies purport to examine the relationship between PCB exposure and some measurable reproductive outcome. As is the case with many compounds, the most instructive studies are those examining occupationally-exposed populations. Individuals in these populations clearly were exposed to the highest levels of PCBs. Unfortunately, only one study of reproductive effects in occupationally-exposed populations has been reported to date. Use and manufacturing restrictions make it unlikely many new studies in this area will become available in the future.

Several studies examined individuals whose only exposure to PCBs came from their environment. Investigations based on "environmentally- exposed" populations have a number of limitations related to their experimental design. A few general comments on these limitations are provided below. These comments are provided prior to any discussion of the actual studies for the purpose of clarifying the major issues affecting the interpretation and extrapolation of the results obtained in these studies. It is hoped clarification will facilitate later discussions dealing with the significance of the studies.

The first problem associated with studies of environmentally-exposed persons is the difficulty of establishing the existence of a dose-response relationship. PCBs are a contaminant common to all persons; therefore it is imperative the exposed population of each study have PCB levels clearly above those considered to be normal or ambient levels. If this cannot be convincingly demonstrated, there is no objective way study findings can be linked to PCBs. Table 4.2.1 contains the reported PCB blood levels of a number of "normal" populations. This table is considered a reasonable reference point from which the magnitude of the PCB exposure reported in the human reproductive studies may be evaluated.

A second problem inherent to the studies of environmentally-exposed

persons is the difficulty of eliminating potential bias from the experimental design of each study. Bias can be introduced by deficient study design, particularly through improper control of logical confounding factors. Studies based upon the consumption of contaminated fish are particularly susceptible to this problem. These studies are confounded by the fact that fish, particularly those from the Great Lakes, contain other persistent chemicals. Several surveys demonstrated measurable levels of organochlorine pesticides and other contaminants in Lake Michigan fish during the late 1970s (the time period when fish consumption was typically evaluated in establishing PCB exposure.) These surveys consistently revealed that Lake Michigan fish at that time contained levels of DDT and related compounds ranging from roughly one-half to more than two-times the PCB levels (Neidermyer and Hickey, 1976; Illinois Dept. of Conservation, 1979;1980). Lake Michigan game fish also contained dieldrin, and in 1977 the levels in lake trout approached the federal action level of 0.3 ppm (Illinois Dept. of Conservation, 1980). Mercury was also found in lake trout and other edible Lake Michigan fish at levels up to approximately one-half the action level, 1 ppm. (Michigan Dept. of Natural Resources, 1979; Illinois Dept. of Conservation, 1980). DDT, dieldrin, and mercury each possess demonstrated adverse reproductive effects in animal studies (Schardein, 1985; OTA, 1985). Selecting only PCBs for consideration as the cause of reproductive effects therefore constitutes an inappropriate and subjective focus.

A related problem of these studies is that the recall of fish consumption is not a reliable index of PCB exposure. This fact is amply demonstrated in two studies (Smith, 1984: Fein et al., 1984), where correlations between PCB blood levels (a measure of dose) and reported fish consumption could not be adequately established. Smith (1984) concluded that the relationship between reported fish-related PCB exposure and serum PCBs *"is so weak that research or PCB risk exposure assessments must never be based solely on the amount of fish in the woman's diet."*

In addition to these inherent problems with fish consumption studies, bias can also be introduced because of limited attempts or inability to control for other confounding risk factors known to affect reproductive function. When studies based upon environmental exposure are poorly matched with respect to

variables of known reproductive significance (e.g., maternal age, consumption of alcohol, drug use, smoking habits, blood lead levels, and even more subtle factors such as educational and socioeconomic status), objective conclusions cannot be reached regarding the causal agent or risk factor that might be responsible for the observed findings.

Some studies of environmental PCB exposure utilized populations with no known source of exposure. In these studies, attempts are made to examine possible PCB effects through correlations between PCB levels (usually within background range) and observed effects. As Rogan and coworkers stated, "... *given the very high prevalence of detectable background [PCB] levels, analysis of a sample in the absence of a specific clinical suspicion of illness is rarely warranted. The most likely outcome of such a test is a positive value that is not readily interpretable. ... There is no body of data that allows clinical interpretation [of PCB levels].*" (Rogan et al., 1985).

An additional, serious limitation to such studies is ambient or background levels of a number of environmentally-persistent chemicals normally found in most or all persons within the U.S. These environmentally-persistent chemicals include the heavy metals and a substantial number of halogenated organic chemicals such as the chlorinated pesticides. Studies which restrict their measurements and attempt correlations to only one of the chemicals common to the blood, body fat and breast milk of humans have no objective basis for determining the causal agent(s) for any observed effects. This problem has been previously noted by Kreiss of the Centers for Disease Control following an attempt to study residents of Triana, Alabama who ate fish contaminated by DDT and PCBs (Kreiss, 1985). To further illustrate this point, Table 4.3.1 summarizes the levels of chlorinated hydrocarbons common to the body fat of the general U. S. population. Each of these chemicals will partition to and can be found in serum and breast milk. Correlations between the tissue levels of one chemical and the tissue levels of a second chemical are both frequent and expected. Many of these chemicals were shown to produce adverse reproductive

Table 4.3.1

Fat Tissue Levels of Halogenated Organics in the Normal Population (ppm)

Residue	Fat Levels By Year									
	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980†
Sample Size	1560	1886	1092	900	779	682	789	827	796	98
Total DDT Equivalents*	8.06	6.97	5.96	5.15	4.76	4.35	3.14	3.52	3.10	2.82
Dieldrin	0.22	0.18	0.17	0.14	0.12	0.09	0.09	0.09	0.08	0.10
Oxychlordane	na	0.10	0.12	0.12	0.11	0.11	0.10	0.11	0.10	0.12
Heptachlor Epxoide	0.09	0.07	0.09	0.08	0.08	0.08	0.07	0.07	0.07	0.08
Nonachlor	na	na	na	na	0.06	0.13	0.10	0.12	0.12	0.14
Benzene Hexachloride	0.35	0.19	0.25	0.21	0.19	0.18	0.14	0.14	0.15	0.12
Hexachloro-benzene	na	na	na	0.03	0.04	0.04	0.04	0.04	0.04	0.04

na = not available
† a subsample
* Total DDT equivalents = DDT + DDD + DDE

Adapted from Stanley and Stockton (1986)

or developmental effects in animal studies, for example DDT, hexachlorobenzene, aldrin, dieldrin, and heptachlor (Schardein, 1985; OTA, 1985). Thus, each chemical common to human fat and serum is a candidate for causation of the reproductive or developmental changes that might be observed in populations whose serum PCB levels are within normal limits. This is a significant oversight, and no meaningful conclusions regarding the causative agent can be objectively reached from any study which fails to recognize and correct for this problem.

Studies of persons occupationally or environmentally exposed to PCBs are discussed in detail in the following sections. Each study was evaluated in terms of the clinical relevance of the purported association, the consistency with which the association has been reported, whether or not confounding factors were controlled, and whether or not a dose-response relationship could be demonstrated. Meaningful determinations can be made only when studies meet these criteria.

4.3.2 Pregnancy Outcome

It appears from a number of studies PCBs can cross the placenta resulting in prenatal exposure. Evidence for this has come from studies in which cord blood was sampled at birth for quantitation of PCBs. Cord blood PCB concentrations are typically significantly lower than the corresponding maternal serum PCB levels. For example, Akiyama et al. (1975) examined 24 matched samples and found maternal blood averaged 2.8 ppb PCBs while the cord blood samples averaged only 1.1 ppb. In a larger study, Jacobsen et al. (1984a) found a mean cord blood PCB level of 2.0 ppb (N = 198), while the mean maternal blood PCB concentration was 4.7 ppb (N = 196). Kodama and Ota (1980) reported mean maternal and cord blood PCB levels for women in each of three years. The results of this study are listed in Table 4.3.2. Similar ratios of maternal serum/cord serum PCB levels were reported by Ando et al. (1985) and Skaare et al. (1988). Somewhat higher absolute PCB values were found in the study by Rogan et al. (1986a), but the relationship between cord and maternal serum PCB concentrations was the same (mean cord serum, <4.27 ppb, N = 744;

Table 4.3.2

Maternal and Cord PCB Blood Levels

	1974	1975	1976	Total
maternal blood (ppb)	5.1 ± 3.0	5.1 ± 3.3	3.6 ± 2.1	4.5 ± 2.9
cord blood (ppb)	1.5 ± 1.3	1.1 ± 0.8	0.8 ± 0.6	1.1 ± 1.0

Adapted from Kodama and Ota (1980)

mean maternal serum 9.06 ppb, N = 872). These results indicate the placenta may serve as a partial barrier to PCBs. Limited data are available regarding the ability of specific PCB congeners to cross this placental barrier, but studies by Ando et al. (1986) suggest that tri- and tetrachlorobiphenyls are more readily transferable than hexachlorobiphenyls.

As a result of this potential intrauterine exposure to PCBs, numerous studies examined the effects of PCBs on human reproduction. Wassermann and coworkers (1982) published a study in which serum concentrations of several organochlorine compounds, including PCBs, were determined in 17 women who had premature deliveries. Ten women with normal third trimester pregnancies served as controls. The average blood concentration of PCBs was higher in the premature delivery group than the control group (71.55 ± 67.28 ppb vs. 19.25 ± 10.32 ppb, mean ± SD), but only eight of the 17 cases of premature delivery were women with PCB blood levels relatively higher than those of the control group. The authors only observed if women in the premature delivery groups also had higher serum levels of several organochlorine compounds including DDT, BHC, dieldrin, and heptachlor epoxide. The authors did not examine variables which might have influenced the gestational time in these groups. For example, heavy smoking is associated with a higher incidence of premature delivery, but smoking was not controlled for in this study. Also, the

authors failed to report the age distribution for the women in the groups compared, a factor with important bearing on the incidence of both premature delivery and higher PCB blood concentrations. Thus, the authors concede in their discussion a cause-and-effect relationship cannot be established based on their data.

These authors also determined PCB concentrations in women with spontaneous or missed abortions and compared these concentrations to control subjects with normal pregnancy. Missed abortion is defined as the retention in the uterus of the products of conception six weeks or more after the death of the fetus. Death of the fetus in missed abortion occurs before the twentieth completed week of gestation. There was no statistically significant difference in serum PCB concentrations between women with spontaneous abortion and the normal pregnancy group (Wassermann et al., 1985).

In the study of women with missed abortions, there were 17 subjects with recent missed abortions (RMA), seven subjects with a history of one or several missed abortions (former missed abortions, FMA), and seven women with normal, second trimester pregnancy (Bercovici et al., 1983). The mean serum PCB concentration was significantly higher in the RMA group than in the control, although approximately half of the women with RMAs had concentrations similar to the controls. The authors divided the RMA group into two subgroups based upon their PCB concentrations -- those with low PCB levels (not different from controls) and those with high levels (Table 4.3.3). There were no differences in the numbers of missed abortions between these groups. Therefore, there were two groups of women with the same PCB concentrations (controls and low PCB concentration RMA group), yet no significant differences in RMAs. There were also two groups of women with the same incidence of RMAs but significantly different PCB levels (low and high PCB concentration RMA groups). These data therefore do not seem to support a role for PCBs in the RMAs.

The authors reported in this study that women with FMA had significantly higher PCB levels than the control women with normal pregnancy. It was not described in the methods sectionof this report how the history of missed abortion

Table 4.3.3

Polychlorinated Biphenyl Serum Levels in Women with Recent and Former Missed Abortions

Peak[1]	Control	Recent Missed Abortions		Former missed abortions
		Low PCB Levels	High PCB Levels	
1 + 2 + 3	1.51 + 1.01	2.09 + 3.06	2.79 + 2.69	1.11 + 1.80
4 + 5 + 6	14.39 + 6.69	17.40 + 6.42	46.47 + 10.6*	51.30 + 11.7*
7			1.22	0.14
8 + 9 + 10	4.79 + 5.01	6.79 + 6.25	51.40 + 20.7*	28.80 + 11.7*
13 + 14			1.20	0.67 + 1.18
Total	20.69 + 10.55	26.29 + 11.60	103.04 + 37.58*	82.00 + 21.40*

[1] Peaks correspond to individual PCB congeners. The identity of these congeners is not specified.
Values expressed as mean ± SD
* $p \leq 0.001$ (Controls versus high PCB level missed abortion and former missed abortion groups).
Adapted from Bercovici et al., (1983).

was established. Unless medical records were used to verify the history of these subjects, the validity of this group may be questioned. Rogan et al. (1985) pointed out women's recall of previous abortions is incomplete, and recall bias may occur if women are alarmed they may have been exposed to a potential toxin. There are other problems with the study which apply equally to the RMA and FMA comparisons. As with the previous Wassermann et al. (1982) study, the variables such as age, etc. which might influence observed associations were poorly controlled. Further, women in the RMA and FMA groups also had significantly higher levels of a number of other organochlorine compounds. It

is therefore impossible to interpret these results as indicating that PCBs cause missed abortion.

Smith (1984) studied the effects of PCB exposure through the consumption of game fish on infant birth weight and health in women from Sheboygan, Wisconsin. Birth weight and gestational age were positively correlated with maternal PCB blood levels, i.e. women with higher PCB levels had a longer gestation time and delivered heavier babies. A positive correlation was also observed for maternal blood PCB concentration and the frequency of illness in the infants during the first four months. Little can be concluded from this study, however, because maternal PCB blood concentrations were apparently independent of the level of exposure (the amount of PCB-containing game fish consumed), and the PCB concentrations in the "exposed" women were in fact lower than those observed for the general population.

Fein et al. (1984a) compared 242 infants born to mothers who consumed moderate amounts of Lake Michigan fish to 71 infants born to mothers who did not consume Lake Michigan fish at all. PCB exposure was based on reported consumption of fish and on PCB levels in cord serum. Some differences in results were obtained depending on which of these two criteria were used to compare the exposed and non-exposed groups. There was agreement between both exposure criteria in that birth weight and head circumference were lower in the PCB-exposed group. While the differences were statistically significant, they were small (e.g. 160-190 g for birth weight, 0.56-0.65 cm for head circumference) and of questionable clinical significance (Table 4.3.4). There was a small but significant change in neuromuscular maturity reported for babies born to fish-eating women, but neuromuscular maturity and physical maturity were not significantly different when PCB blood levels were the basis for comparison. Possibly one factor contributing to the observed birth weight difference was the fact that the gestational age of the babies in the exposed group was five days shorter than the non-fish eating group. One criticism of this study is the exposed and unexposed groups were not well-matched with respect to other variables which might affect birth weight (Table 4.3.5). For example, the exposed group had three times the percentage of women who consumed alcohol during pregnancy. This group also had higher percentages of other concurrent

Table 4.3.4

Adjusted Birth Size and Gestational Age Measures by Overall Contaminated Fish Consumption and Cord Serum PCB Level

value	Overall Contaminated Fish Consumption: Non-Fish Eaters (n = 71)	Fish Eaters (n = 242)	P
Birth weight (kg)	3.66 ± 0.54	3.47 ± 0.53	<0.05
Head circumference (cm)	35.48 ± 1.36	34.92 ± 1.31	<0.01
Gestational age (based upon last menstrual period)(wk)	40.82 ± 3.07	40.31 ± 2.97	
Gestational age (Ballard examination) (wk)	39.85 ± 1.42	39.15 ± 1.40	<0.01
Neuromuscular maturity	19.96 ± 2.48	18.52 ± 2.44	<0.001
Physical maturity	17.13 ± 2.25	16.67 ± 2.19	

	Cord Serum PCB level: < 3 ng/ml (n = 166)	≥ 3 ng/ml (n = 75)	P value
Birth weight (kg)	3.57 ± 0.54	3.41 ± 0.54	<0.05
Head circumference (cm)	35.28 ± 1.18	34.63 ± 1.19	<0.001
Gestational age (based upon last menstrual period)(wk)	41.03 ± 3.01	39.77 ± 3.06	<0.05
Gestational age (Ballard examination) (wk)	39.41 ± 1.40	39.47 ± 1.41	
Neuromuscular maturity	19.95 ± 2.42	19.00 ± 2.40	
Physical maturity	16.96 ± 2.14	16.94 ± 2.15	

Adapted from Fein et al. (1984a)

Table 4.3.5

Control Variables Yielding Differences for Exposed vs. Non-Exposed Infants

	Exposed	Non-Exposed	P value
Overall contaminated fish consumption[1]			
Maternal prepregnancy weight (kg)	62.0 ± 11.6	66.1 ± 14.7	<0.10
Type of deliver (% spontaneous)	67.4	77.5	<0.05
Alcohol prior to pregnancy (%)	54.2	28.2	<0.001
Alcohol during pregnancy (%)	22.7	7.0	<0.01
Caffeine[2] prior to pregnancy (%)	40.1	28.2	<0.10
Caffeine[2] during pregnancy (%)	22.7	12.7	<0.10
Cold medications during pregnancy(%)	28.6	13.2	<0.01
Cord serum PCB level[3]			
Maternal age (yr)	27.1 ± 5.3	26.0 ± 4.2	<0.10
Weight gain during pregnancy (kg)	12.7 ± 4.6	13.8 ± 4.6	<0.10
Type of delivery (% spontaneous)	63.2	73.5	<0.10

[1] Fish consumption: exposed defined as ≥ 11.8 kg over 6 years, n=242; nonexposed n = 71.
[2] Equivalent of > 2 cups of coffee per day.
[3] Exposed defined as ≥ 3.0 ng/ml, n=75; nonexposed n=166.

Adapted from Fein et al. (1984a)

exposures during pregnancy, such as caffeine consumption and the use of cold medications. A second criticism is the average maternal PCB serum level for this group was 5.5 ± 3.7 ppb and the average serum cord PCB level was only 2.5 ± 1.9 ppb. Thus, the entire study population had serum PCB levels in the low end of the range of values reported for unexposed populations (see Table 4.2.1). A third criticism is the failure to take into account fish from Lake Michigan are contaminated with a number of organochlorine compounds, particularly DDT. Thus, the potential the reported associations might also be shown to exist for the serum levels of other chemicals common to these women was not addressed. Lastly, in a second report by Jacobson et al. (1985) which examined 123 infants (92/123 were in the fish-eating category), the reported significant differences in birth weight and head circumference of infants born to fish eaters or non-fish eaters are considerably smaller (i.e. 89 g and 0.1 cm, respectively), and are apparently not significantly different for the two groups.

Taylor et al. (1984) looked at 388 pregnancies in 354 women who worked at capacitor manufacturing plants. Information for this study was obtained from birth certificates and hospital records. The women were divided into two groups, high-exposure and low-exposure, depending on the location of their job in the plant. The birth weights for offspring of the women in the high-exposure group were on average 153 g lower than those for the low-exposure group but this difference was not significant at the $P < 0.05$ level. When birthweights were adjusted for gestational age, there was no difference between exposure groups. When maternal smoking and alcohol consumption were included in the analysis, there were no differences between groups in birth weight or gestational age. Further, there was no association between high homolog serum PCB concentrations and birth weight or gestational age (Taylor et al., 1984).

4.3.3 Lactation

Rogan et al. (1987) studied the duration of breast-feeding in 858 women in North Carolina, many with elevated PCB levels from undetermined causes. DDE levels were also elevated in many of these women, and attempts were made to correlate DDE or PCB concentrations in breastmilk with duration of lactation. Both DDE and PCB concentrations were negatively correlated with duration of

lactation, meaning that women with higher levels tended to wean their child sooner. There were many reasons given for stopping breast-feeding, including social and occupational reasons that could not possibly be related to PCB exposure. Further, many other variables correlate deither positively or negatively with duration of lactation, including education level, age, smoking status, etc., making it impossible to attribute shorter lactation specifically to PCBs. Among the many reasons for weaning, lactational failure (defined as insufficient milk, poor infant weight gain, infant allergic to milk, baby had difficulty breast-feeding, baby became ill) was a category that might reasonably be caused by chemical exposure. When analysis was restricted to cases of lactational failure, there was no association with PCB levels.

4.3.4 Developmental Studies

Jacobson et al. (1984b) also published a report evaluating neonatal behavioral deficits in children born to women who had eaten contaminated Lake Michigan fish in comparison with those who had not eaten contaminated fish. Though not explicitly stated in the report, these would appear to be the same neonates examined in the Fein et al. (1984a) paper. Behavioral status was evaluated by the Brazelton Neonatal Behavioral Assessment Scale (NBAS). all but three (out of 287) of the newborns, testing was performed on day three after birth. For purposes of statistical analysis, the 44 items of this scale were reduced to seven summary clusters. Attempts were made to control variables other than exposure which might influence results. A total of 36 variables were examined, including demographic background; maternal prepregnancy weight and height; sex of infant; parity and gravidity; stress during pregnancy; prenatal care and diet; weight gain during pregnancy; alcohol, caffeine, and nicotine consumption before and during pregnancy; delivery complications; obstetrical medication; age (in hours) at NBAS examination; and cord serum levels of polybrominated biphenyls (PBBs). The strongest statistical relationships for contaminated fish consumption were with clusters classified as relating to autonomic maturity, number of abnormal reflexes, and range of state (Table 4.3.6). Maternal consumption of contaminated fish was highest for neonates classified as "worrisome" in these three clusters. It was not established whether these behavioral effects were lasting or transitory. While

contaminated fish consumption correlated with these behavioral deficits, cord serum PCB levels did not. Thus, the association would appear to be due to something other than PCBs in the contaminated fish.

Table 4.3.6

Worrisome Performance on Three NBAS Clusters by Contaminated Fish Consumption

Cluster	Non-Exposed Controls	High Exposure (>6.5 kg/yr)	χ^2
1. Autonomic Maturity			
Normal	64	67	
Worrisome	1	6	3.18*
2. Reflexes			
Optimal or normal	55	48	
Worrisome	10	24	4.97**
3. Range of State			
Optimal, normal, or labile	64	65	
Worrisome (flat, depressed)	1	7	4.16**

NBAS = Neonatal Behavioral Assessment Scale
* $p < 0.10$, ** $p < 0.05$

Adapted from Jacobson et al. (1984b)

Jacobson et al. (1985) examined children born to mothers in Grand Rapids, Michigan to study the possible association of umbilical cord PCB levels with the occurrence of subtle neurological changes. The test population consisted of 123 white, predominantly middle-class infants. Approximately 75% (92/123) of the mothers of these infants were considered to be moderate to heavy consumers of PCB-contaminated Lake Michigan fish. The other mothers did not eat these fish. The seven-month old infants were tested for their ability to recognize visual stimuli. In this test, the children were exposed to a visual target, and later during the procedure were simultaneously re-exposed to the same target and a

novel target. Visual recognition was defined as the percent of visual fixation on the novel target. The authors stated there was a statistically significant dose-effect relationship between cord PCB levels and fixation of the novel target. Children born to mothers with cord serum PCB levels of 0.2-1.1 ng/ml fixed their gaze on the novel target approximately 61% of the time. Infants born to mothers with cord serum PCB levels of 1.2-2.2, 2.3-3.5, and 3.6-7.9 ng/ml had visual fixation percentages of approximately 60%, 57%, and 50%, respectively. The difference between the fixation times of infants in the high cord serum PCB group and the two low cord serum PCB groups was statistically significant ($p < 0.05$). The possible effect of confounders such as demographic background, pregnancy and delivery complications, stress, diet, smoking, alcohol, and caffeine exposure were factored into the analysis. The authors suggested while their study indicates high cord PCB levels may be associated with developmental delay in the performance of a visual task, the results of this study cannot be extrapolated to indicate that any permanent PCB-induced damage had occurred. Indeed, postnatal exposure to PCBs in breast milk did not correlate with changes in visual recognition memory. Although the authors accounted for a number of confounding variables in their analysis, one obvious oversight was the failure to include an evaluation of serum or cord lead concentrations. Considerable evidence suggests lead may induce subtle changes in learning and behavior in children born to mothers with slightly elevated blood lead concentrations, and the study of Jacobson et al. (1985) is flawed for failing to consider the potential effect of this important environmental contaminant.

As part of the North Carolina Breast Milk and Formula Project, Rogan et al. (1986b) looked for potential effects of prenatal exposure to PCBs and dichlorodiphenyl dichloroethane (DDE). This exposure was estimated by determining the concentration of PCBs or DDE in maternal milk fat at birth. Birth weight and head circumference at birth were taken from the infant's chart or measured directly. Neonates were administered the NBAS in the first (59%), second (20%), or third (16%) week of life. To facilitate comparison with the results of Jacobson et al. (1984b), individual scales were divided into the same seven clusters. Decreased birth weight was associated with maternal weight, sex, and maternal smoking, but not with PCB or DDE levels. Head circumference was also unaffected by PCB or DDE levels, as was

hyperbilirubinemia. Of the various NBAS cluster scores, only the tonicity and reflex scores were affected by PCB and DDE levels. PCB levels were associated with less muscle tone and activity, but only at the higher concentrations (Table 4.3.7). Similarly, hyporeflexia was associated with PCB levels, but only for the highest concentrations (Table 4.3.8). If analysis is restricted to neonates administered the NBAS within three days of birth, as has been recommended for this examination, the trends remain the same but only hyporeflexia was statistically significant. Two important precautions must be considered in interpreting the results of this study. Hyporeflexia was associated with both PCBs and DDE. It is therefore impossible to determine if hyporeflexia is the result of exposure to PCBs, DDE, or some other substance for which these compounds serve as a marker. Also, as noted by the authors, the NBAS is an evaluation of the infant when newborn and is generally not strongly predictive of later findings. Therefore, the NBAS cannot distinguish between lasting and transient behavioral abnormalities.

Many of the infants in the Rogan et al. report of 1986b were followed for one year to determine if PCB (or DDE) exposure via breast milk was associated with adverse health consequences. Health effects were evaluated by infant weight and frequency of physician visits for various illnesses. PCB exposure for breast-fed babies was calculated using measured PCB milk levels, information regarding the length of breast-feeding, and assumptions as to milk fat content and amount of breast milk consumed per day. PCBs appeared to have no effect on growth as determined by body weight gains. The most common ailments resulting in a physician visit were upper respiratory tract infections (colds, flu, sore throat, etc.), otitis media, and gastroenteritis (diarrhea, vomiting, etc.). As stated by the authors, *"None of these diseases showed any evidence of harmful effects of PCBs or DDE; in fact, the trends usually were in the opposite direction."* Data from this study relating to method of feeding, PCB exposures, and incidence of illness appear in Table 4.3.9.

Table 4.3.7

Association of PCBs with Tonicity Cluster Score and Its Components

PCB Level	No. of babies	Tonicity cluster score (%<5)	Activity scale (%<4)	General tone scale (%<5)
0.0 - 0.99	49	10.2	10.2	6.1
1.0 - 1.49	241	7.1	6.6	2.5
1.5 - 1.99	276	10.9	8.3	3.3
2.0 - 2.49	151	13.9	6.6	6.0
2.5 - 2.99	66	12.1	6.1	7.6
3.0 - 3.49	34	8.8	5.9	0.0
3.5 - 3.99	20	20.0	10.0	10.0
4.0 +	29	20.7	17.2	10.3

PCBs given as ppm in milk fat at birth
Adapted from Rogan et al. (1986b)

Table 4.3.8

Association of PCBs with Abnormal Reflexes

PCB Level	No. of babies	Abnormal reflexes (%4+)	Low reflexes (%4+)
0.0 - 0.99	49	12.2	8.2
1.0 - 1.49	241	10.4	6.2
1.5 - 1.99	276	14.1	8.3
2.0 - 2.49	151	14.6	9.3
2.5 - 2.99	66	13.6	9.1
3.0 - 3.49	34	14.7	8.8
3.5 - 3.99	20	25.0	25.0
4.0 +	29	27.6	17.2

PCBs given as ppm in milk fat at birth
Adapted from Rogan et al. (1986b)

Table 4.3.9

Per Cent of Children Ever Having Upper Respiratory Infection (URI), Otitis Media (Ear), or Gastrointeritis (GI) in Various Age Intervals by Feeding Method and Contaminant Amounts

	mg	No. of Children	% Ever Having URI	% Ever Having Ear	% Ever Having GI
0 - 3 Months					
Bottle-feeders		80	16	18	24
Ex-Breast-feeders		--	--	--	--
Breast-feeders		689	21	11	11
PCBs					
	0 - 1	74	36	22	27
	1 - 2	194	20	14	11
	2 - 3	238	22	9	8
	3 - 5	145	13	8	6
	5 +	38	11	5	16
3 - 6 Months					
Bottle-feeders		80	28	33	13
Ex-Breast-feeders		172	35	39	14
Breast-feeders		503	24	22	6
PCBs					
	0 - 1	71	37	25	10
	1 - 2	180	24	29	5
	2 - 3	164	23	14	6
	3 - 5	51	12	14	4
	5 +	37	16	22	3
6 - 12 Months					
Bottle-feeders		80	48	58	25
Ex-Breast-feeders		321	54	63	29
Breast-feeders		353	49	52	17
PCBs					
	0 - 1	54	33	50	17
	1 - 2	84	62	65	21
	2 - 3	95	48	48	15
	3 - 5	69	54	47	16
	5 +	51	41	47	18

For each time period, children are divided into bottle-feeders, ex-breast-feeders, and current breast-feeders. Current breast-feeders are further divided by the estimated amount (mg) of PCBs consumed during the time period. Entries are the percent of children ever having the disease during the time period. Diseases are upper respiratory infections (URI), otitis media (ear), and gastroenteritis (GI).

Adapted from Rogan et al. (1987)

4.3.5 Male Reproduction

Attempts were made to examine the effects of PCBs on male reproductive function by indirect means. Bush et al. (1986) reported the results of a study in which semen samples were collected from fertile , subfertile, infertile and post-vasectomized men. Semen samples were analyzed for 74 PCB congeners, p,p'-DDE, mirex, and hexachlorobenzene. Sperm motility, count, and morphology were also determined. Thirty-two PCB congeners were detected in the semen samples, although in low concentrations (mean total PCB residue of 5.8 ppb). No difference between fertility groups could be discerned for total PCBs (sum of all congeners), p,p'-DDE, mirex, or hexachlorobenzene. Some individual PCB congeners were higher in the vasectomized group. When the vasectomized group was excluded from analysis, there was no association between PCB congener concentration and either sperm count, motility, or percentage of normal forms. There was also no association when sperm count and motility were combined and considered jointly. When the PCB congeners were analyzed statistically for each of the individual remaining groups (fertile, subfertile, infertile), an association emerged between three congeners (2,4,5,2',4',5'- and 2,4,5,2',3',4'-hexachlor- obiphenyl, and 2,4,5,3',4'-pentachlorobiphenyl) and sperm motility in the infertile group. The authors conclude, with a probability > 0.99, that sperm motility is inversely related to the concentrations of these three congeners in samples with low sperm counts. The authors do not attempt to explain why these congeners would have this effect only in low sperm count samples. They state:

> *Reduction of sperm motility with increasing PCB concentration may indicate a causative affect [sic] of the PCB congeners themselves, or it may be an indication of the effect of a more potent series of associated compounds such as the tetrachlorodibenzo-furans. On the other hand, the association may not indicate a causative relationship, it may only indicate something less tangible, such as an urban lifestyle.*

Emmett et al. (1988) conducted a health survey of switchgear workers exposed to PCBs. All participants were male, and part of the survey asked if the workers had ever been tested for infertility. In some of the positive responders, the couple had a child after testing or the problems were found to exist in the wife. When these were excluded from the analysis, 3/56 were tested in the

exposed group while 1/56 was tested in an unexposed control group. This difference was not significant. The incidence of testicular atrophy was also found to be unrelated to PCB exposure.

4.3.6 Summary of Reproductive and Developmental Studies

Studies of reproduction in humans exposed to PCBs are limited, and many cannot be interpreted. The studies conducted in populations occupationally exposed to PCBs were least ambiguous in that the exposure to PCBs was substantial and generally without significant exposure to other chemicals. These studies found no adverse effect of PCBs on gestation, birth weight, or male reproduction.

Women studied by Rogan and colleagues in North Carolina had documented higher-than-normal PCB levels, but results were sometimes confounded by elevated DDE levels. By including DDE in the analysis of their data, these investigators found no adverse effects on gestation, birth weight, neonatal behavioral effects, or infant health that could be attributed to PCBs.

Serious flaws prevent conclusions from the remaining studies regarding possible effects of PCBs on reproduction or development. Most of these studies were poorly controlled with respect to variables known to influence reproduction, e.g. maternal age, consumption of alcohol and drugs during pregnancy, smoking, and blood lead levels. A number of studies involved PCB exposure based upon participant recall of past consumption of contaminated Lake Michigan fish. In these studies, it was not demonstrated that the "exposed" group had PCB levels greater than the controls, and in fact the PCB concentrations in the "exposed" group were in the low-normal range reported by other investigators. Further, contributions from other, potentially-toxic contaminants found in the fish were ignored. In view of these study limitations, it cannot be concluded exposure to PCBs results in adverse effects on human reproduction or fetal and neonatal health. In fact, the current limited evidence indicates no reproductive effects of PCBs at levels of exposure occurring occupationally or environmentally.

In view of these study limitations, it cannot be concluded environmental exposure to PCBs results in any adverse effect on human reproduction or fetal and neonatal health.

4.4 CLINICAL STUDIES

4.4.1 Description of Studies in Occupationally-Exposed Workers

The occupational setting is perhaps the best indication of the potential health effects caused by PCBs because of the high levels of exposure and the longevity of the exposure for some of the persons in these study populations.

Wolff (1985) has reviewed occupational exposure to PCBs and summarized the results of several studies. Table 4.4.1 contains examples of air and skin wipe PCB levels reported in occupational studies. This type of exposure can result in substantial PCB blood concentrations. Table 4.4.2, also taken from the review of Wolff (1985), contains examples of blood PCB concentrations measured in exposed workers. Adipose tissue concentrations in occupationally-exposed individuals typically are approximately 100-times higher than the serum PCB levels. Table 4.4.3 contains examples of adipose and blood PCB concentration results from occupational studies.

PCB exposure in the occupational setting probably occurs primarily by dermal and inhalation routes, although it is unclear which predominates. Lees et al. (1987) have recently calculated theoretical doses received from both inhalation and dermal routes using a number of assumptions and measurements of airborne and surface PCB levels in work areas. They also observed work practices in transformer service and repair for opportunity for dermal contact with PCBs. PCB intake from the dermal route was estimated to be four orders of magnitude higher than from the inhalation route. They concluded that transformer service and repair workers receive PCBs predominantly by the dermal route, and speculated that the dermal route is the primary source of PCB exposure in other situations involving PCBs at room temperature.

PCB exposure in the occupational environment may occur to varying degrees. The report by Mosely et al. (1982) suggests that workers who serviced PCB-filled transformers in indoor vaults may have been exposed to relatively high levels of PCBs. The evidence for this exposure is indirect, and it is based on measurements during servicing and repair operations which indicate air levels

Table 4.4.1

PCBs Determined From Skin of Exposed Workers (Aroclor 1242 or 1016)

Air levels ($\mu g/m^3$)	Skin wipe ($\mu g/cm^2$)	Exposure	Reference
80 - 275	2 - 22	Capacitor manufacture	(1)
0 - 264	0.1 - 7	Electrical equipment manufacture	(2)
0.4 - 9	0.05 - 5	Transformer inspection	(2)
< 100	0.002 - 0.019	Capacitor manufacture, off worksite	(3)

Refs: (1) Brit. J. Ind. Med. 38:49, 1981; (2) Brit. J. Ind. Med. 39:361, 1982; (3) Anal. Chem. 56:1492, 1984.
Adapted from Wolff (1985)

Table 4.4.2

PCB Levels in Blood of Exposed Workers (Aroclor 1016/1242/1248)

Air Levels (mg/m^3)	Blood Levels (ng/ml) mean	high	N	Exposure	Ref.
0.3 - 2	1060[a]	3500	19	"inside"	(1)
	440[a]	1400	14	"out"	(2)
0.05 - 0.275	130[a]	407	60		(2)
0 - 0.26	355[b]	3330	26	exposed	(3)
	149[b]	1500	55	ever exposed	
	89[b]	370	140	never exposed	
0.1 - 1	118[b]	2530	110	high exposure	(4)
	48[b]	604	180	other	

[a] whole blood
[b] geometric means, serum or plasma

Refs: (1) Arch. Environ. Health 31:189, 1974; (2) Brit. J. Ind. Med. 38:49, 1981; (3) Brit. J. Ind. Med. 39:361, 1982; (4) Int. Arch. Occup. Environ. Health 49:199, 1982.
Adapted from Wolff (1985)

Table 4.4.3

PCB Blood Levels (Aroclor 1254) and Duration of Exposure

Duration of employment (yr)	Mean blood concentration (ng/ml)	N	Mean adipose concentration (μg/ml)	N	Reference
12 ± 6	238	80	--	--	(1)
16 ± 8	24[a] 6[b]	258 32	17 4	53 8	(2)
17	33[c]	86	5.6	36	(3)
3.8	14[d]	15	1.4	5	
4.3	12[e]	19	1.3	9	

[a] persons with more than 5 years employment; geometric mean; geometric mean of 53 plasma samples which matched the adipose samples was 54 ng/ml.
[b] persons with less than 5 years employment; geometric mean.
[c] persons exposed.
[d] persons nominally exposed.
[e] nonexposed.

Refs: (1) Brit. J. Ind. Med.38:49, 1981; (2) Int. Arch. Occup. Environ. Health 49:199, 1982; (3) Ambio 3:70, 1974.
Adapted from Wolff (1985)

much higher than current OSHA standards. Though the air levels are high during this activity, the duration of contact is typically short. Exposure of these workers is therefore probably modest when compared to PCB exposures of workers involved in some other facets of capacitor or transformer manufacture.

During the first 35 years of PCB manufacture and industrial use there were apparently only three reports of PCB-related occupational illness (Brown et al., 1981). The first reported incident occurred in 1933 at the Swann Chemical Company, the original U.S. manufacturer of PCBs (Jones and Alden, 1936). There was an almost simultaneous occurrence of chloracne skin eruptions in 23 of 24 men working in the manufacture of PCBs. The skin changes resembled adolescent acne with blackheads and pustules lasting for several months. The men also complained of lassitude, but were without clinical signs of ill health.

Jones and Alden (1936) concluded that the problem was probably related to impurities in the benzene feedstock, since skin eruptions began when a new source of crude benzene was used and disappeared when this use stopped and the process equipment was better enclosed. Two more incidents of PCB exposure producing chloracne were reported in the early 1950's and 1960's. Meigs et al. (1954) reported that 7 out of 14 persons developed chloracne after being exposed to PCB vapors (reported as 100 $\mu g/m^3$) coming from a leaky heat exchanger. There was a similar incident in 1964, in which 13 of 16 people developed chloracne when exposed to vapors coming from an oven in which PCB-plasticized enamels were baked (Brown et al., 1981).

One of the most recent occupational studies is that of Ouw et al. (1976). In this report Ouw and coworkers examined 34 workers from a single capacitor plant using Aroclor 1242. The PCB exposure periods for this group of workers were one year of exposure (31/34) and more than five years exposure (16/34). The control population consisted of 30 persons (23 males + 7 females) who ranged from 21 to 50 years of age. The worker population consisted of 15 men and 19 women ranging from 33-55 years of age. Nineteen (14 men and five women) of the capacitor worker group worked in the impregnation room where the inside of the capacitor casing was impregnated with Aroclor 1242. In this process, exposure to the heated Aroclor (70°C) could be excessive unless impervious gloves were worn and an efficient exhaust system was working. The second group of employees (1 man and 14 women) assembled Aroclor-dipped capacitor components. Here the major route of exposure was clearly dermal. No job rotation was practiced at this plant. The average PCB blood levels of the capacitor workers and the control group are provided in Table 4.4.4. The blood Aroclor levels are reported as ppb based on measurements taken for four different chromatographic peaks. Standards for this analysis were prepared from Aroclor 1242. Concentrations of the congeners corresponding to three of the four peaks were roughly equivalent. One congener (retention time 1.31) was present in lower concentrations. The reason for this lower concentration is unclear, although greater metabolism and elimination of this unknown congener could account for this difference. According to the four PCB peaks monitored, the exposed group had average serum PCB levels of approximately 400 ppb, a value substantially greater than the non-detectable levels of the unexposed control group. The clinical tests measuring liver function revealed

Table 4.4.4

Blood Aroclor Levels in Capacitor Workers

Group	Blood Aroclor Level (ppb) (Retention Time Relative to Aldrin) 0.69	1.31	1.47	1.96
Control	N.D.	N.D.	N.D.	N.D.
Exposed	394 ± 460	198 ± 258	415 ± 429	475 ± 718

Adapted from Ouw et al. (1976)

that bilirubin, alkaline phosphatase, albumin, SGPT, and immunoglobulins from the factory workers were within the normal limits for each test (Table 4.4.5). The industrial hygiene practices at this plant were poor, and air monitoring revealed that the air concentrations were 0.32, 1.08, 1.44, and 2.22 mg/m^3 for the soldering area, the general atmosphere near the tank, the atmosphere near the unloading tank in front of the exhaust register, and the area near the unloading tank away from the exhaust register, respectively. The allowable air standard at this time was only 1.0 mg/m^3. One case of chloracne and five eczematous rashes were reported among exposed workers at this plant. The major complaints were burning of the eyes, face, and skin. Given the fact that no significant health effects were observed in workers whose blood PCB levels were below 200 ppb, the authors proposed using 200 ppb as a tentative upper limit of acceptable blood PCB levels. The exhaust system used to ventilate the impregnation room was improved and gloves were recommended for the workers, but two months later no lowering of serum PCB levels was achieved. On the contrary, the average blood PCB level in the 15 workers sampled after the ventilation system had been improved had increased, suggesting to the authors that the new dermal protective equipment (i.e. gloves) was not being used.

Table 4.4.5

Comparison of Hepatic Function Tests Between the Exposed Workers Employed Inside and Outside the Impregnation Room

Clinical Test	Normal Values	Impregnation Workers	Other Workers
Bilirubin (μmol/l)	1.7-20.5	5.7 ± 2.9	6.1 ± 1.8
Alkaline Phosphatase (μmol/l)	20-85	60.7 ± 12.3	62.9 ± 17.4
SGPT (I.U.)	5-35	21.4 ± 17.8	28.6 ± 18.1
Total protein (g/l)	63-79	76.8 ± 4.9	72.1 ± 4.6
Albumin (%)	62.5 ± 6.5	61.5 ± 5.1	62.4 ± 2.7
α-1 globulin (%)	4.2 ± 1.1	3.6 ± 0.6	3.6 ± 0.5
α-2 globulin (%)	7.9 ± 2.4	9.4 ± 1.8	9.3 ± 1.1
β globulin (%)	10.4 ± 3.6	11.9 ± 1.5	10.6 ± 1.8
γ globulin (%)	15.1 ± 4.6	13.4 ± 2.9	14.0 ± 2.1

Adapted from Ouw et al. (1976)

Probably the most extensively studied population of occupationally-exposed workers were the 326 workers employed at two capacitor plants. Detailed studies of the health of these individuals have been released in a number of reports. These studies may represent the best indication of the health issues associated with occupational exposure, as 40% of the 326 persons included had been employed for 20 years or longer. The actual breakdown of the employment histories of these individuals at these plants was: 10.1% had worked for five years or less, 20.9% had worked for 5-10 years, 17.5% had worked 10-15 years, 11.4% had worked for 15-20 years, 29.1% had worked for 20-25 years, and 11% had been employed for more than 25 years. The long-term employee exposure had been to Aroclors 1242 and 1254, but two years prior to the initiation of the study, Aroclors 1016 and 1221 had replaced other Aroclors in the plant (Fischbein et al., 1979).

Wolff (1982) determined the body burden of PCBs in a number of these 326 capacitor workers. Two hundred ninety plasma samples and 61 adipose biopsies were analyzed. The average age of the employees was 42 years for the male population and 48 years for the female population, with about a 15-year average employment record for both sexes. The adipose levels of PCBs in these workers ranged from 0.6-414 ppm for the lower PCB homologs (LPCBs, similar to Aroclor 1016 or 1242) and from 1-165 ppm for the higher PCB homologs (HPCBs, similar to Aroclor 1254 in composition). The geometric means for all persons were 28 ppm (HPCBs) and 14 ppm (LPCBs), respectively. The range of plasma concentrations were 6-2,350 ppb for the lower PCB homologs and 0-546 ppb for the higher homologs. Persons directly involved with capacitor treatment, the high exposure category (air levels of 500-940 $\mu g/m^3$), had adipose tissue levels that ranged from 18-414 ppm, geometric mean of 102 ppm, and plasma PCB levels ranging from 45-1,349 ppb, with a geometric mean of 218 ppb. The adipose:plasma partition coefficient for PCBs was 160 for the HPCBs and 190 for the LPCBs.

Examination of the health of these workers revealed that the prevalence of eye or upper respiratory irritation was 48%; 13.8% of the group had experienced a cough and 10% a tightness in the chest during their normal work routine. There was decreased vital capacity in 14% (34/243 examined) of the group

compared to a rate of only 5.6% in the normal population (Warshaw et al., 1979). Of these, only 7 demonstrated a generalized airway obstruction while 80% (27/34) were diagnosed as having a restrictive pattern of impairment. While the restrictive pattern was an unusual finding, it was not observed at all in the nonsmoking group of women (Warshaw et al., 1979). Given this inconsistency, the significance of this observation remains open to question unless verified by other studies.

The results of a longitudinal study of this same population do not support these initial findings of pulmonary dysfunction. Spirometry studies were conducted in 1976, 1979, 1981, and 1983 by Lawton et al. (1986). The initial study (1976) consisted of 194 workers; subsequent studies consisted of only 136 workers because of incomplete data on some individuals. In 1976, 16% of the workers were reported to have restrictive impairment, but chest x-rays did not suppor this type of impairment. These findings were similar to those found by Warshaw et al. (1979), who found a prevalence of 14% of restrictive impairment in workers from the same plant. In contrast to the finding in 1976, spirometry measurements in 1979 indicated that the percent of the population with restrictive impairment had declined to 2.2%. Because of the inconsistencies in the data and the fact that restrictive pulmonary pathology is non-reversible, the 1976 data was re-evaluated. It was found that 8% of the 1976 spirometric tests had been inadequately performed, as opposed to an error rate of 1% or less in subsequent studies. The data generated in 1979 and 1983 indicated a continuing improvement in the the reliability of the spirometric measurements with experience of both the test operator and the workers. Thus, the 1976 data were considered to be artifactual due to test operator inexperience and inadequate expiratory efforts. Also observed in 1976 was an association between high PCB exposure in the workplace and decreased FEV_1/FVC (FEV_1= forced expiratory volume at one second; FVC = forced vital capacity), but only in females. There was no significant association between serum PCB level and spirometric parameters in 1979 for either sex. Thus, the results of the longitudinal study do not support a relationship between pulmonary dysfunction and PCB exposure.

Histories taken from the workers revealed the following: chloracne had occurred in 10.7% of the 326 workers; 39.3% had suffered some kind of a rash;

24.8% had complained of a burning sensation; and hyperpigmentation, thickening of the skin, or discoloration of the finger nails each occurred in less than 4% of the workers. Gastrointestinal complaints were also reported by 18% of the workers. Most common among the G.I. symptoms were weight loss, 9.5%; loss of appetite, 4.8%; and nausea, 4.2%. Subjective neurologic symptoms reported by the workers included : headache, 27.8%; dizziness, 13.9%; depression, 12%; memory loss, 8.2%; fatigue, 22.8%; nervousness, 31%; sleeplessness, 10.8%; and drowsiness, 11.4%. Physical examination of the workers also uncovered a prevalence of dermatologic abnormalities. Approximately 50% of the workers reported having had some type of skin problem including redness, swelling, dryness, and a thickening of the skin. On initial examination in 1976, 12% of the 310 employees examined had oculodermatologic symptoms, including edema of the upper eyelid (1.6%), injected conjunctiva (5.5%), eye discharge (2.3%), hyperpigmentation (1.3%), and enlargement of the Meibomian glands (1.3%) (Fischbein et al., 1985). In a later examination of 181 of the employees in 1979, the overall incidence of eye symptoms was similar, with 13.3% of the workers displaying one or more of the above symptoms (see Table 4.4.6). Given the fact that these workers had higher

Table 4.4.6

Occulodermatological Findings in PCB Workers

Conditions	PCB Workers 1976 (n = 310)	PCB Workers 1979 (n =181)	Yusho (n = 189)	Yu-Cheng (n = 130)
Edema(upper eyelid)	1.6%	2.2%	73%	58.9%
Injected conjunctiva	5.5%	8.3%	70.8%	60.1%
Eye discharge	2.3%	1.7%	85.7%	80.5%
Hyperpigmentation	1.3%	0%	----	66.6%
Enlargement of Meibomian glands	1.3%	1.1%	----	70.1%

Adapted from Fischbein et al. (1985)

PCB blood levels than those with Yusho and Yu-Cheng, and yet were found to have fewer dermal problems, the authors suggested that dibenzofurans were probably responsible for the Yusho and Yu-Cheng poisoning episodes (Fischbein et al., 1985). Based on their results and experience, the authors felt that severe clinical effects are relatively rare in occupationally-exposed persons and differ considerably in degree of severity from the Japanese and Taiwanese poisonings.

The results of the clinical chemistry investigation of the individuals comprising this study were generally unremarkable, and the researchers commented on the *"paucity of abnormal results"* (Fischbein et al., 1979). As can be seen in Table 4.4.7, the percentage of samples outside the normal range was small and these data can be considered a reflection of the type of random test results to be expected when 321 persons are tested without a control group (i.e. without obtaining some indication of the variability occurring in the normal population). An elevation of cholesterol was the most frequent "abnormality." However, cholesterol elevation is common in about 30% of the population with advancing age, and 66% of this study group were older than 40. To emphasize the inconsistent nature of the clinical chemistry findings, one only has to compare the transaminase data. Fewer people were outside the "normal range" for gamma-glutamyl transpeptidase (N=6), the most sensitive liver function test, than had "abnormally high" SGPT levels (N=23). This and the variability in the number of values outside the normal range among tests suggests that there was no trend to these findings. The average PCB plasma concentration in all workers was still 172 ppb, even years after Aroclor 1016 and 1221 had been installed, and for the high exposure group 354 ppb.

In the article by Fischbein et al. (1982), 289 of the original 326 workers were re-examined for dermatological problems. The plasma PCB values for 42 individuals showing clinical evidence of a skin problem were correlated to their dermatological problems. When using a Student's t-test adjusted for unequal variances, a significant difference was found between the mean concentrations of the higher homologs of PCBs for the male workers only. But no statistically significant differences were observed if non-parametric tests were used. Furthermore, when attempts were made to correlate the dermatological abnormalities and clinical parameters of liver function such as serum bilirubin,

Table 4.4.7

Distribution of Pertinent Clinical Chemistry Parameters in 321 PCB-Exposed Workers

Biochemical Parameters

BUN	≤20	20-25	*25+
Number (percent)	250 (77.9)	54 (16.8)	17 (5.3)
Creatinine	≤1.5	1.5-1.7	*1.7+
Number (percent)	270 (84.2)	38 (11.8)	13 (4.0)
SGOT (IU/l)	≤50	*50-74	*75+
Number (percent)	314 (97.8)	6 (1.9)	1 (0.3)
SGPT (IU/l)	≤50	*50-74	*75+
Number (percent)	297 (92.8)	20 (6.3)	3 (0.9)
LDH (IU/l)	≤250	*250-275	*275+
Number (percent)	313 (97.5)	7 (2.2)	1 (0.3)
Alkaline phosphatase (IU/l)	≤50	*50-75	
Number (percent)	317 (98.8)	4 (1.2)	
γ-glutamyl transpeptidase (U/l)	≤40	*40-59	*60+
Number (percent)	315 (98.1)	5 (1.6)	1 (0.3)
Bilirubin (mg/100 ml)	≤1.0	1.0-1.3	
Number (percent)	304 (94.7)	17 (5.3)	
Cholesterol (mg/100 ml)	≤250	250-200	*300+
Number (percent)	165 (51.4)	99 (30.8)	57 (17.8)
Triglycerides (mg/100 ml)	≤199	*200-249	*250+
Number (percent)	282 (89.5)	16 (5.1)	17 (5.4)
Total lipids (g/100 ml)	0.5-0.8	0.8-1.0	*1.0+
Number (percent)	283 (88.2)	27 (8.4)	11 (3.4)

*Indicates a value outside the normal range.

Adapted from Fischbein et al. (1979)

SGOT, SGPT, alkaline phosphatase, LDH, cholesterol, or total lipids, no significant association was found.

Other follow-up studies examined the PCB disposition in 26 of the original 326 capacitor workers. The median PCB fat concentration was 33 ppm for the isomers being studied, and the adipose to blood ratio varied considerably with congener. This partition ratio ranged from as low as 50:1 (adipose : blood) for the 2,4,5,2',5'-pentachlorobiphenyl isomer to as high as 370 for the 2,3,5,6,2',4',5'-heptachlorobiphenyl isomer. The average ratio for total PCBs was estimated to be about 190:1 (Wolff et al., 1982a). A preferential bioaccumulation was noted for congeners with chlorines in the 2,4 and 3,4 positions, which was partly related to differences in the metabolism and partition ratio. For example, 2,4,4'-trichlorobiphenyl was the PCB congener in highest concentration in the fat of 20/26 of the workers; however, it should also be noted that this is the PCB congener in the greatest concentration in Aroclor 1016, the Aroclor these workers were most exposed to over the last five years of work-related exposure. Of considerable toxicological interest was the finding that the 3,4,3',4'-tetrachlorobiphenyl isomer could not be detected in these individuals even though it has been determined to be present at low levels in Aroclor mixtures. This evidence suggests that perhaps this isomer is not bioaccumulative in humans (Wolff et al., 1982a).

A number of other relatively recent, but less exhaustive studies of occupationally-exposed worker populations have been reported. Maroni et al. (1981a&b) have reported a study of Italian employees working in two capacitor plants using commercial PCB mixtures from 1949 to 1965. These mixtures were the equivalent of Aroclor 1254, and after 1965 the plants used Pyralene 3010 and Apirolio, which are equivalent to an Aroclor 1242. The mean ($\pm$ SD) age and employment duration of the 80 employees examined for PCB blood concentrations were 37 ± 8 years and 12 ± 6 years, respectively (Maroni et al., 1981a). PCB measurements taken of their workroom air, tools, and hands showed that air PCB concentrations ranged from 0.048 to 0.275 mg/m^3, that surfaces and tools in the workplace were heavily contaminated (0.2-159.0 $\mu g/cm^2$), and not surprisingly, the palms of the employees' hands contained PCBs at levels of 2-28 $\mu g/cm^2$. The corresponding blood PCB levels ranged from

88 ppb to 1,319 ppb. Workers in the impregnation room had the highest average blood levels, i.e. 556±337 ppb, but the average blood levels in high-power assembly workers (406±173 ppb), low-power assembly workers (361±189 ppb), filter workers (246±130 ppb), and general maintenance workers (400±114 ppb) were not much lower. The authors pointed out the obvious dermal absorption risk to these workers and the fact that the gas chromatographic pattern of air concentrations tended to be enriched with the lower-chlorinated biphenyls (i.e. those isomers with the greatest volatility) while surfaces contained more pentachlorobiphenyl and other heavier-chlorinated biphenyls.

Of these 80 workers, 14 had dermatologic problems that were probably work related: four had chloracne, four had folliculitis, one had oil dermatitis, and five had irritative or allergic dermatitis. The workers with chloracne all worked in the impregnation room of plant A. The mean blood PCB level for these workers was 450 ppb and was not significantly different from the five unaffected workers employed in the same area. Sixteen of the workers were reported to have hepatic involvement as determined by hepatomegaly or an elevation in a liver function test value. There was, however, no correlation of hepatic findings to duration of exposure or to total PCB blood levels (see Table 4.4.8). There was no specific pattern to the liver function tests reported as being outside the normal range, and none of the elevations were of a magnitude sufficient enough to indicate a significant liver function problem (e.g. all alkaline phosphatase, serum electrophoretic patterns, bilirubin, and urinalysis values were normal). Furthermore, an age-paired control group comprised of persons from the area was not included in this study, a deficiency further complicating any attempt to interpret the significance of the minor changes reported in this study. None of the workers diagnosed as having liver abnormalities had ever suffered chloracne, and a number of different health problems were described in these workers that may have contributed to the minor clinical findings reported. Thus, it appears evident upon review of these data that the changes noted were not remarkable and do not appear to be related to PCB exposure.

More recently, Maroni et al. (1984) examined this worker population in an attempt to determine whether PCB exposure resulted in an induction of microsomal enzymes or abnormalities in porphyrin metabolism. The authors

Table 4.4.8

Clinical Findings in Capacitor Workers Exposed to Pyralene Or Apirolio

Age (yrs)	Exposure index (yrs)	Hepato-megaly	Clinical tests[a] AST <12	ALT <12	SGGT 6-28	SOCT 0.5-10	SPCH 18-36	Blood PCB levels (ppb)
Plant A								
52	10.9	++				11		691
50	13.7	+						1319
44	6.2	++			34			611
51	2.6	+++				10.2		672
39	2.5	+	20	13	49	17.2	39	643
26	0.3	+				15		1259
31	1.3	-			39	11.7		277
38	3.1	-	13			13.7		438
Plant B								
30	4.0	+		21.8	33			470
30	2.5	++			53			377
56	11.0	++		20				180
24	2.5	++						131
26	2.5	++		23.6	49			376
30	4.0	+		18.2	48			290
31	2.0	+	25.4	36.4	91			152

[a]AST = serum aspartate aminotransferase; ALT = serum alanine aminotransferase; SGGT = serum gamma glutamyltranspeptidase; SPCH = serum pseudocholinesterase; SOCT = serum ornithine-carbamoyltransferase; - = absent, + = mild, ++ = moderate, +++ = pronounced

Adapted from Maroni et al. (1981b)

used serum levels of gamma glutamyl-transpeptidase and urinary D-glucaric acid excretion as indices of hepatic enzyme induction. Urinary porphyrin concentration was established by measuring porphyrinic homologues having four to eight carboxylic groups. Each of these parameters was elevated in the exposed group as compared to controls. However, changes in these parameters did not correlate with blood PCB concentrations.

Chase et al. (1982) performed a cross-sectional study on 120 male workers exposed to PCB fluids in a locomotive maintenance and repair facility. The purpose was to determine the prevalence of increased PCB absorption among exposed workers and to determine what, if any, clinical findings were associated with exposure. The 120 individuals were divided into three groups -- exposed, nominally-exposed, and nonexposed -- based on the frequency of their contact with the PCB liquids. This classification put 86 persons in the exposed group, 15 in the nominally-exposed group, and 19 in the nonexposed group. Each group had a different age distribution, the nonexposed and nominally-exposed groups having more young employees. The average age of the exposed group was 41.4 years, that of the nominally-exposed group was 37.2 years, and the nonexposed group was 30.7 years. As might be expected, the average length of employment was also skewed, with the exposed group averaging 17 years compared to 3.8 and 4.3 years in the other two groups. A review of the medical histories and physical findings failed to reveal evidence of organ toxicity in the exposed group, although several cases of chloracne had occurred over the years. Chloracne and other dermatological findings were more prevalent in the exposed group, but no significant association could be demonstrated between these findings and PCB levels. There was no statistically significant difference between the groups for their serum levels of triglycerides, cholesterol, HDL cholesterol, SGOT, SGPT, and GGTP, although there was a slight trend in the GGTP values. These results have been provided in Table 4.4.9. The PCB plasma levels in the nominally-exposed and nonexposed groups ranged from 10-30 ppb while in the exposed group the values ranged from 10-312 ppb; however, no average values were provided in this report. Likewise, in the exposed group PCB levels in fat tissue ranged from 1-21.6 ppm while the PCB levels in the nominally and nonexposed individuals averaged only 1.3 and 1.4 ppm and coincided with that of the normal population.

Table 4.4.9

Averages of Selected Biochemical Parameters in 120 Workers by PCB Exposure Category

Parameter	Exposed	Nominally Exposed	Nonexposed
Triglycerides, mg/dl	135.8	128.7	145.5
Cholesterol, mg/dl	231.7	238.3	238.2
HDL cholesterol, mg/dl	58.8	57.2	61.7
SGOT, IU/l	19.6	19.1	19.4
SGPT, IU/l	21.7	21.6	21.3
GGTP, IU/l	37.1	34.1	29.8

Adapted from Chase et al. (1982)

Smith et al. (1982) examined employees at three occupational sites. The first, an electrical equipment manufacturing plant, had an average air PCB concentration of 81 $\mu g/m^3$. Skin smear wipes of selected workers showed that from 10 to 688 μg PCBs/100 cm^2 accumulated on the skin of the workers over the course of a work shift. The second site, a public utility company apparently using Aroclor 1254, had personal air sample measurements of 37-215 $\mu g/m^3$. The third site, a private utility company, was sampled and found to have air PCB levels in its underground transformer vaults of 0.4-82.3 $\mu g/m^3$, skin wipe samples from two employees showed 5 and 487 $\mu g/100\ cm^2$, and surface levels ranging from non-detectable to 800 $\mu g/100\ cm^2$. A summary of the numbers of

employees, the measures of exposure, and the serum PCB concentrations for each site appears in Table 4.4.10. No consistent patterns or abnormalities were noted upon physical examination of the workers at any site. A number of associations between serum PCB levels and the results of clinical measurements were reported; however, normal or control values were not provided. When the confounding variables of age, sex, and site were taken into account, associations between serum levels of either lower chlorinated PCBs (four or fewer chlorines) or higher chlorinated PCBs (five or more chlorines) and the following clinical biochemistries were noted : serum log SGOT values, GGTP values, cholesterol, log HDL-cholesterol, and log triglyceride. No clinical significance was attached to any of these associations. The absence of overt clinical dysfunction in these individuals and those in similar studies was noted by the authors, who state in their conclusions (Smith et al., 1982):

> *These correlations occur in the absence of overt clinical dysfunction identifiable on physical examinations. The simultaneous changes in SGOT, GGTP, plasma triglyceride, and HDL-cholesterol are evidence of an effect on the liver and exposure to PCB, the biological significance of which is not clear. A positive correlation between serum GGTP and triglyceride has been described as has the rise of serum GGTP in the presence of drugs known to induce liver microsomal enzymes. ... ...*
>
> *Therefore, alterations in liver enzyme tests in association with increasing serum PCB concentrations may not themselves be predictive of future chronic disease but may reflect liver microsomal enzyme induction. ... ...*
>
> *In general, a lack of clinically apparent illness among workers with high levels of exposure to PCB and high serum PCB concentrations seems to have been the rule. ...*
>
> *One would expect the adverse human health consequences from exposure to PCB, if they exist, would most readily be identified in groups with the greatest exposures (excluding poisoning attributable to accidental contamination of food). None of the published occupational or epidemiological studies (including ours), however, have shown that occupational exposure to PCBs is associated with any adverse health outcome, to be distinguished from demonstrable subclinical biochemical alterations. An exception to this is the occurrence of chloracne during the early years of its use, and possibly currently as well, depending on circumstances of its use and exposure.*

Hara (1985) studied the health status of workers at a capacitor factory in Shiga Prefecture in Japan, where Kanechlor-500 and Kanechlor-300 were used. Blood samples collected in 1973, one year after the use of PCBs was discontinued

Table 4.4.10

Descriptive Data from the Study of Smith et al. (1982)

Site	Employees[a] exposed/total	Exposures skin wipes[b]	Exposures personal air[c]	Range of serum L-PCB[d] exposed	Range of serum L-PCB[d] non-exposed	Range of serum H-PCB[e] exposed	Range of serum H-PCB[e] non-exposed
Manufacturing plant[f]	144/288	10-688	–	8-3330	1-370	7-250	1-110
Public Utility[g]	14/47	–	37-215	5-52	1-59	7-24	1-19
Private Utility	25/46	5-487	3.1-82.3	9-48	12-52	7-250	2-25

[a] exposed/non-exposed based on type of work performed, i.e. whether or not likely to have contact with PCB-containing material.
[b] $\mu g/100\ cm^2$
[c] $\mu g/\ m^3$
[d] L-PCB = lower chlorinated PCBs (primarily those with 4 or fewer chlorines)
[e] H-PCB = higher chlorinated PCBs (primarily those with 5 or more chlorines)
[f] Aroclors 1242 and 1016 used
[g] Aroclors 1254 and 1260 used

at the plant, contained about 30 ppb average for men and 21 ppb for women handling Kanechlor-300 alone. Workers handling both Kanechlors had higher blood PCB levels, about 70 ppb for men and 99 ppb for women. Retired workers surveyed had comparable blood PCB levels. During the time when PCBs were being handled in the plant, dermatologic complaints were common. About 40% of the employees exposed to PCBs had black comedones and chloracne and 13% had skin irritation and erythema. These symptoms declined continuously after PCB use was discontinued. Other than complaints of stomach upset, nausea, and heartburn, no other symptoms associated with PCB exposure appeared. Clinical biochemistry studies of the workers revealed only an elevated serum triglyceride which did not correlate with blood PCB levels.

Takamatsu et al. (1984; 1985) determined the plasma PCB concentrations in a total of 112 workers at three sites in 1976-77. Two of the sites were involved in the manufacture of silk thread and the third site manufactured marine paint. Plasma PCB concentrations in workers ranged from approximately 2 to 500 ppb. Clinical examination of 26 of the workers found acneform lesions in six of them

(two of which were adolescent). One worker had subjective complaints of fatigue, heavy-headedness, paresthesia, and joint pains, etc. A follow-up clinical examination in 1982 revealed that this patient was suffering from organic solvent intoxication, and that no clinical symptoms attributable to PCB exposure had emerged in the other workers.

Emmett (1985) has published a study of switchgear shop employees involved with transformer maintenance functions. Thirty-eight current employees and 17 previously exposed employees were included in the study, and their measurements were compared to those of 56 non-exposed individuals. Adipose and serum PCBs in the currently exposed workers ranged from 0.2-33.0 ppm and 1-300 ppb, respectively (with a geometric mean of 2.1 ppm adipose and 12.2 ppb serum), while in previously-exposed workers adipose levels ranged from 0.3 to 5.1 ppm and serum ranged from 1 to 30 ppb (geometric means of 0.83 ppm and 5.9 ppb, respectively). By comparison, non-exposed persons had adipose tissue levels of 0.2-3.0 ppm (mean of 0.6 ppm) and serum levels of only 1-15 ppb (mean of 4.6 ppb). Several clinical biochemical parameters were determined and compared to a non-exposed group (operating engineers). These comparisons revealed small but statistically significant differences in serum albumin, serum LDH, and serum T_4 levels when the values for nonexposed persons were compared to the exposed group (4.66 vs 4.55, 186.8 vs 202.3, and 8.8 vs 8.24, respectively). However, none of these small changes were associated with any clinical symptoms in this study, and as can be seen in Table 4.4.11, attempts to correlate log adipose or serum PCB levels to test values found no associations in every instance except for urinary 17-OH steroids and SGGT. Thus, there was no PCB-related trend for any of the variables reported to have small but significant differences in the exposed group, and no significant differences were noted between the groups for those two parameters that appear to correlate with PCB levels (borderline significance [$p = 0.055$] was noted for 17-OH steroids). In contrast to a number of other studies, serum lipids in the PCB-exposed group (current and former employees combined) were not different from those in the non-exposed group (see Table 4.4.12), but log serum PCB concentrations did correlate with log triglyceride, cholesterol, and log VLDL (see Table 4.4.13).

Table 4.4.11

Pearson Correlation Coefficients for PCB Concentrations and Laboratory Results*

Liver Function Log of Variable	Log Adipose PCBs Correlation coefficient	p value	Log Serum PCBs Correlation coefficient	p value
total protein	0.163	NS	-0.028	NS
abumin	-0.086	NS	-0.022	NS
bilirubin	-0.108	NS	-0.138	NS
alkaline phosphatase	0.140	NS	0.177	NS
SGOT	-0.106	NS	0.096	NS
SGPT	-0.195	NS	-0.053	NS
SGGT	0.086	NS	0.194	0.045
serum T4	-0.109	NS	-0.009	NS
urinary ALA	-0.108	NS	-0.028	NS
urinary 17OH steroids	-0.315	0.002	-0.146	NS
urinary coproporphyrins	-0.099	NS	-0.080	NS
urinary uroporphyrins	0.002	NS	-0.169	NS
antipyrene half-life	-0.131	NS	0.023	NS

* results were not corrected for possible confounding variables
Adapted from Emmett (1985)

Table 4.4.12

Serum Lipid Concentrations

Variable (mg/dl)	Arithmetic or Geometric Mean Exposed group	Nonexposed group
triglycerides	116	128
total cholesterol	191	197
HDL cholesterol	43	40
LDL cholesterol	120	126
VLDL cholesterol	23	25

* geometric mean used for values with log normal distribution (Note : none of these variables were significantly different at the $p < 0.05$ level)
Adapted from Emmett (1985)

Table 4.4.13

Pearson Correlation Coefficients for PCB Concentrations and Serum Lipid Levels

Log of Variable	Log Adipose PCBs		Log Serum PCBs	
	Correlation coefficient	p value	Correlation coefficient	p value
triglycerides	-0.019	NS	0.259	0.007
total cholesterol	0.031	NS	0.202	0.036
HDL cholesterol	0.063	NS	0.053	NS
LDL cholesterol	0.021	NS	0.143	NS
VLDL cholesterol	-0.010	NS	0.270	0.005

Adapted from Emmett (1985)

Based on these observations, Emmett proposed that PCBs may preferentially partition with plasma lipids. Such a phenomenon would explain the positive correlations observed in a number of studies between serum triglyceride levels and serum PCB concentrations. It would also undermine the assertion that this correlation indicates that PCBs alter lipid metabolism. As can be seen in Tables 4.3.12 and 4.3.13, rather than serum PCB levels influencing serum triglyceride concentrations through an effect on lipid metabolism, serum triglyceride levels appear to dictate (all other factors being equal) serum PCB concentrations by increasing the serum:adipose partitioning coefficient and shifting PCBs from adipose tissue stores to the blood compartment.

The relationship between serum PCB levels and serum lipid concentrations has also recently been examined by Brown and Lawton (1984). Their analysis confirms that serum PCB levels are dependent upon serum lipid levels, and indicates that serum PCB levels may not provide an accurate estimate of PCB body burden. They suggest instead that a determination of the concentration of PCB in serum lipid provides an indication of adipose tissue levels and therefore of body burden.

In a study of individual PCB congeners, Guo et al. (1987) further confirmed

the influence of serum lipid and albumin concentrations on the partitioning of PCBs between serum and adipose tissue. In this study, seven PCB congener peaks were evaluated in the following groups of workers: 35 men currently exposed to PCBs in transformer maintenance and repair, 17 men with past exposure at these tasks in the same shop, and a comparison group of 56 similarly skilled men with the same employer who had never been occupationally exposed to PCBs. Transformer repair workers were exposed mainly to Aroclor 1260 and to lesser amounts of Aroclor 1242. Stepwise regressions of log serum congener concentration on log adipose congener concentration and numerous serum and biological parameters were performed. Only cholesterol, albumin, and average servings of fish per day were significant for at least one congener peak. Log serum congener concentration was consistently correlated with log adipose congener concentration for the four congeners of highest molecular weight (2,3,4,2',4',5'-hexa-, 3,4,5,3',4'-penta-, 2,3,4,5,2',3',4'-hepta-, and 2,3,4,5,2',3',4',5'-octachlorobiphenyl). By comparing the correlation coefficients (R squares) for the equation relating serum congener concentration to adipose congener concentration with equations that also include cholesterol and albumin (in addition to adipose concentration as predictors of serum PCB), it could be determined whether or not cholesterol and albumin contribute significantly in predicting the variability of serum PCB levels. Using this aprroach, it was found that cholesterol and albumin can influence the distribution or partitioning of PCBs between serum and adipose tissue.

In a separate report, Emmett et al. (1988) reported the results of clinical examinations of the group of switchgear shop workers described above. A number of neurobehavioral and irritant symptoms were more prevalent in the exposed group but were probably not related to PCB exposure. For example, eye irritation and tearing were more prevalent in the exposed population; however, on examination, abnormal findings of conjunctivitis or tearing were found in only one exposed worker. Considering the low volatility of PCBs, a more likely cause of these complaints was exposure to 1,1,1-trichloroethane, a solvent used in spill clean-up. Wheezing was more frequent in exposed workers, but physical examination of the chest was normal and wheezing was not associated with either exposure or smoking when one was adjusted for the other.

Mucocutaneous symptoms such as those found among Yusho victims were not found, and diagnosable chloracne was not observed. Two exposed workers reported a history of melanoma; no cases were observed in the comparison group, but the difference in incidence was not statistically significant. Exposed and nonexposed groups also did not differ in response to antigens that measure delayed hypersensitivity.

Fischbein (1985) has recently reviewed the liver function test results of his previous studies of 326 capacitor workers and compared and contrasted these findings to those observations made in poisoned persons with Yusho and Yu-Cheng. During the 1940's and 1950's these capacitor workers were exposed primarily to Aroclor 1254 and 1242. In 1972 the capacitor fluid was changed to Aroclor 1016 and 1221 which contained some chlorinated benzenes and an epoxide compound as a stabilizer. Air measurements revealed PCB air concentrations of 0.007 mg/m^3 in the lowest exposure areas, about 0.41 mg/m^3 in the quality control and equipment testing areas, to a high of 0.9 to 11.0 mg/m^3 in the areas where the capacitors were immersed in the dieletric fluids and then washed. As in other capacitor plants, PCB exposures resulted primarily from the inhalation of fumes coming from the heated PCB fluids and dermal contact with contaminated surfaces. The first study was conducted in 1976; in 1977 PCB fluids were discontinued and were replaced by a dielectric fluid composed of dioctyl phthalate and chlorinated benzenes. In December of 1979 a follow-up study of these workers was performed. The employment profile of the study population was listed as: 32% had worked 0-9 years, 31% worked 10-19 years, and 37% had worked for more than 20 years. Some 64% of the workers were 40 years of age or older, and 35% were 50 years of age or older. Table 4.4.14 provides a breakdown of serum PCB levels by sex and degree of chlorination. The liver function tests for these individuals are listed in Table 4.4.15. Although some of the minor differences between the sexes were statistically significant, the values for all test results were well within the normal limits for each test. More importantly, the number of persons outside the normal range for each test varied from 0-7%. Thus, the prevalence of abnormal results was comparable to that reported for the general population (Fischbein, 1985). After completing Pearson correlation coefficients between liver function tests and PCB levels, no

Table 4.4.14

Plasma Levels of Lower (LPCB) and Higher (HPCB) PCB Homologs in 230 Capacitor Workers

PCB	Levels (ppb)	Male (N)	Female (N)	Total Workers (N)	Total Workers (%)
LPCB	0-99	85	66	151	65%
	100-199	28	17	45	20%
	> 200	23	11	34	15%
HPCB	0-24	68	60	128	56%
	25-74	50	24	74	32%
	> 75	18	10	23	12%

Adapted from Fischbein, (1985)

Table 4.4.15

Liver Function Tests in 230 Capacitor Workers

Test (IU/ml)	Females (N =112)	Males (N = 144)
SGOT	24.8 ± 11.4	27.1 ± 10.8
SGPT	25.5 ± 13.1	31.2 ± 13.5
Alkaline phosphatase	25.6 ± 8.7	26.2 ± 6.9
LDH	175.9 ± 30.8	167.1 ± 25.7
GGTP	10.8 ± 7.5	15.7 ± 9.0

Adapted from Fischbein, (1985)

clear associations were found. In females, but not males, log LDH levels were significantly correlated to log HPCB and log total PCB levels. In males, but not females, log GGTP levels were negatively correlated with log HPCB levels. A preliminary analysis of the data collected in the follow-up study indicated more abnormal GGTP values. However, inclusion of retirees into these calculations eliminates the statistical significance of both correlations. Also, as pointed out by Guzelian (1985), GGTP is easily influenced by so many factors, including the consumption of alcohol, that relatively small changes have little diagnostic value. Given the fact that evidence of liver injury is not likely to show such sex-linked preferences for the test found abnormal, the weakness of the correlations, and the fact that retirees eliminate the statistical significance of the findings, no evidence of liver dysfunction is provided by these studies. On the contrary, the paucity of abnormal results still remains as the major observation.

Lawton et al. (1985a) have also examined this same capacitor worker population. The authors identified a study population consisting of three relatively high exposure groups, those who worked in capacitor filling areas of high PCB air levels (high exposure group), those whose jobs did not involve direct contact with PCBs but who were on the periphery of the high exposure area (low exposure group), and those maintenance workers who had brief high exposure and contact (medium exposure group). At the time of the 1976 study this population consisted of 152 males and 42 females. The mean service time of the workers was 17 years (2-35), and the average age was 40 years (20-65). Interestingly, only 33 of this study population were included in the 326 volunteers reported on by Fischbein et al. (1979). In the 1979 follow-up study, Lawton and coworkers' "directly exposed population" had been reduced to 174 total employees. The authors felt that air levels of PCBs during the years of 1954-1977 when Aroclor 1242 and 1016 were in use were probably at least the 0.69 mg/m^3 observed in 1975, with extensive dermal contact occurring as well. The worker population was evaluated by review of medical records and by clinical laboratory measurements. The battery of clinical laboratory tests was extensive, including at least 42 separate measurements. PCB exposure was also evaluated by measuring serum PCB levels. These serum levels were expressed as total PCBs based on the measurements of selected chromatography peaks, separately as low-chlorinated (LPCB) and high-chlorinated PCBs (HPCB), as total PCBs

based upon the sum of the LPCB + HPCB, and as the serum lipid PCB values. The authors examined these and other independent variables (e.g. age, smoking, etc.) in a three-tiered approach in an attempt to identify associations. The first analysis was a simple linear regression, which was followed by a multiple linear regression. Finally, a backward stepwise linear regression was used to remove non-significant independent variables.

In the 1976 examination, the mean serum lipid LPCB content was 93 ppm (15-560 ppm, 5-95% confidence limits), corresponding to an estimated average body burden of 2.0 grams (0.3-12.3 g) for the mean population body weight (77 kg). Regression analysis for length of service and PCB levels found no assocation, suggesting that steady state levels had been achieved within the first few years of employment. The mean serum HPCB level was estimated to be 8 ppm (2-34 ppm), which corresponds to an average body burden of 0.2 grams (0.04-0.7 g). The mean LPCB body burden estimated from the 1979 follow-up study performed 29 months after PCB use was discontinued was only 0.4 g (0.7-2.0 g). This suggests that 80% of the LPCBs had been cleared during this time and that the half-life for these homologs is on the order of one year. Similar estimations were not analytically feasible for the HPCBs.

An association between PCBs and decreased bilirubin, elevated serum GGTP, and elevated lymphocyte levels was noted in the first examination, but of these only an elevation in monocytes was confirmed by the second examination. Although log serum PCBs were positively associated with serum triglyceride and cholesterol levels, this association disappeared when serum PCB levels were expressed as levels in serum lipids. Thus, this study provides additional evidence that serum PCB levels are a function of serum lipid levels. The authors noted that the clinical health of the study population was good and the mortality experience normal despite such risk factors as obesity and smoking. The authors also concluded that the paucity of clinical findings was consistent with laboratory studies involving chronic Aroclor 1242 exposure to rats which have produced comparaole tissue PCB levels. These studies have observed no overt symptoms of clinical poisoning and no pathological evidence of liver damage.

Acquavella et al. (1986) assessed the health effects of a group of workers employed at a capacitor manufacturing plant. Of the 500 employees of the plant, 205 participated in the study. The average length of employment for the study group was 12.9 years. The dielectric fluids used over the course of time were Aroclor 1242 (1941-1971), Aroclor 1016 (1971-1977), and dioctyl phthalates (1977-present). An industrial hygiene survey conducted in 1982 found that PCB levels on workplace surfaces ranged from 5 to 1,700 $\mu g/100\ cm^2$. Subsequent to the survey, areas with levels exceeding 100 $\mu g/100\ cm^2$ were decontaminated to a level below 100 $\mu g/100\ cm^2$. Mean (geometric) serum PCB levels among the workers were 18.22 ± 2.88 (S.D.) ppb with a range of 0 to 424 ppb. More than 70% of all workers had serum levels below 3 ppb.

Physical examination of the workers revealed no liver or skin abnormalities that might be attributable to PCB exposure. Significant correlations between the log serum PCB level and cholesterol level, log systolic blood pressure, log diastolic blood pressure, log GGTP, log triglycerides, lactic dehydrogenase, and log SGOT were observed. None of these correlations were significant, however, after adjusting for age and sex, though partial correlations of log serum PCB with cholesterol and GGTP were of borderline significance ($p = 0.08$ and 0.10, respectively).

Multiple linear regression analysis found duration of employment, cumulative occupational exposure, cumulative fish consumption, and cholesterol level to be significant predictors of serum PCB levels. Although cholesterol was a significant predictor of serum PCB levels, it could not be determined from this analysis whether the PCB level influences the cholesterol level or whether the serum PCB levels are dependent upon the level of the serum lipid. Other studies indicate that the PCB level in serum is influenced by the lipid levels in blood (Brown and Lawton, 1984; Guo et al., 1987).

Seppalainen et al. (1985) attempted to determine whether PCBs produce neurotoxicity in occupationally exposed workers. The workers in this case were individuals assigned to clean up after an explosion destroyed 15 capacitors in a plant. It was estimated that no more than 300 liters of PCBs escaped from the capacitors, and that approximately 100 liters underwent pyrolysis. The extent of

pyrolysis of PCBs, and no doubt other materials, is indicated by the description in the report that "*... firemen had to search for the explosion site for half an hour within the smoke.*" Clean-up workers complained of headaches, odd feelings, pin and prick sensations, itching, or odd temperature feelings in their arms or legs. Sixteen workers were selected who were considered to have been extensively exposed to the PCBs. Nerve conduction velocities were measured in these subjects. The specific parameters measured included maximal motor conduction velocity (MCV) of the median, ulnar, and deep peroneal nerves on the right, sensory conduction velocity (SCV) of the right sural nerve, and distal SCVs of the right median and ulnar nerves. Measurements were taken two and six months after the explosion and compared with results from age-matched controls. At two months after the explosion, 4/15 exposed workers had normal SCVs, and 7 of the remaining 11 had slightly abnormally slow conduction velocities in one or two nerves. All individual conduction velocities were within the normal limits on the second examination (six months). Surprisingly, the authors concluded that PCBs seem to exhibit neurotoxic properties in humans. Such a conclusion is unwarranted for a number of reasons. To begin with, the effects that they report appear to be slight and transient. Also, changes in nerve conduction velocities were not correlated with serum PCB concentrations. Further, the extensive combustion at the site indicates the probable formation of pyrolysis products of PCBs (including dibenzofurans) and other potentially toxic combustion products. And finally, the presence of significant levels of toxicants besides PCBs at the clean-up site should have been obvious in that the symptoms reported by the workers were vague (headaches) or not considered to be associated with PCB exposure (pin and prick sensations, itching, odd temperature feelings in their arms or legs).

Some conclusions reached by two recent reviews summarizing the evidence provided by the various clinical studies in occupationally exposed workers are noteworthy and will be reiterated here (Brown et al., 1981; Gaffey, 1981). First, while higher exposures to PCBs tend to mean a higher body burden, there was a general lack of correlation between exposure duration and body burden. Second, although not all studies agree, there was also a suggestion that the higher-chlorinated PCBs were more likely to accumulate in adipose tissue, suggesting a slower metabolism rate. Third, the general health of the

occupationally-exposed group was considered to be good.

Gaffey (1981) summarized the results of 17 epidemiological studies of health effects of PCBs. While clinical details were not provided, two of these studies (not described above) concluded that the workers were in good health despite high exposures (up to 1900 ppb blood PCB levels in one study). Of 15 studies reporting clinical measurements, 11 reported dermatologic effects, nine reported liver function tests, six reported lipid measurements, and five reported on blood chemistry. Gaffey concluded that while no clear correlation between PCB blood levels and chloracne was provided, the studies suggested that when PCB blood levels exceed 150 to 200 ppb, chloracne might occur. He also concluded that dermatitis, like chloracne, was a frequently observed effect, and that it might be associated more with the body levels of the higher chlorinated PCB compounds. Of the nine reported studies of liver function, only five found some mild change in liver function tests. No consistent pattern was identified, nor was an association between these changes and PCB blood levels ever found. No adverse health effect was associated with PCB exposure in any of the studies. In the six studies in which lipid metabolism was considered, the most consistent change observed was an elevation in serum triglyeride. However, as Emmett (1985) has observed, this may reflect an influence of triglycerides on PCB partitioning rather than an effect by PCBs on lipid metabolism. Of the five studies of blood chemistry, none reported any relationship between the tests and PCB blood levels. Of the two studies that measured blood pressure, one found no association while one reported an association between PCB levels and diastolic blood pressure (Gaffey, 1981).

The appearance of histopathologic lesions in the livers of laboratory animals exposed to PCBs has generated considerable concern that PCBs may be hepatotoxic in man. Many of the clinical biochemical parameters incorporated into the epidemiological studies described above were specifically for the purpose of assessing PCB effects on liver function, and the results of these tests deserve some additional comment. A number of studies noted statistically significant changes in indices of liver function, but the magnitudes of these changes were uniformly quite small. Small changes in these parameters can reflect other physiologic processes besides toxicity. For example, there is evidence that

serum transaminase activities, e.g. SGGT, and serum triglycerides may be increased during enzyme induction (Whitfield et al., 1972; Martin et al., 1975; Emmett, 1985; Guzelian, 1985). PCBs have been shown to cause hepatic enzyme induction in both laboratory animals and in occupationally-exposed workers (Alvares, et al., 1977). Other common exposures, e.g. alcohol consumption, can also produce mild changes in these parameters (Guzelian, 1985). Therefore, while substantial, consistent alterations in the parameters used to evaluate liver function would clearly indicate liver injury, the minor changes and inconsistent patterns observed after PCB exposure cannot be concluded to be a consequence of hepatotoxicity (Emmett, 1985; Guzelian, 1985).

Of interest regarding the interpretation of occupational exposure studies is the Rosenberg et al. (1987) analysis of the validity of self reported occupational histories in PCB-exposed workers. Worker recall of PCB-exposure-related job history was compared to company records and "validity" was indexed according to worker age, duration of employment, diversity of jobs, worker sex, and interviewer. Mean non-validity was 25% with considerable variability, and the only independent predictor of validity was job diversity (not surprisingly, fewer jobs per individual correlated with higher validity). The authors concluded that self reporting may have fallen short of what was necessary to ensure dependable relative risk estimates for PCB exposure. Such a finding has relevance to occupational and epidemiological studies which attempt to assess previous chemical exposures by personal interviews. Persons with short employment duration and/or high job diversity may confound the results of mortality and other comparisons because these job characteristics are poorly correlated with exposure validity as illustrated by Rosenberg et al. (1987).

In summary, a review of the human data from studies of occupationally exposed persons, while demonstrating that PCBs caused dermal problems, failed to identify any significant clinical disease associated with electrical grade PCBs (Fischbein et al., 1979; Smith et al., 1982; Brown et al., 1981; Gaffey, 1981; Drill et al., 1982; Emmett, 1985; Kimbrough, 1987). Even though some physiologic changes were noted, no clinical significance could be attached to any of these changes.

4.4.2 Summary of Occupational Exposure to PCBs

The highest and longest PCB exposures to humans have occurred in the occupational setting. Serum PCB concentrations in workers roughly 100 times those observed in the general population have been reported. The study of these workers probably represents the best opportunity for determining adverse health effects of PCBs in humans. Several cohorts of occupationally exposed workers have been examined for the presence or history of physical illness and have been subjected to a variety of clinical laboratory measurements. The only physical symptoms that could be conclusively attributed to PCBs were chloracne and other dermatological lesions in workers exposed to high levels of PCBs. One study (Warshaw et al., 1979) reported diminished respiratory function, but groups were poorly matched for the important variable of smoking status, and the results of a longitudinal study of this population indicated that the initial findings were artifactual due to test operator inexperience and inadequate expiratory effort (Lawton et al., 1986). Several studies have used clinical laboratory tests to measure liver function status in PCB-exposed workers. The results were generally negative. When changes were noted they were uniformly small and of questionable clinical relevance. Further, changes in one clinical test of liver function were generally not supported by other measurements of liver function in the same study. Such minor and inconsistent abnormalities would be anticipated in any large study of a healthy population, and the data therefore do not indicate clinical hepatotoxicity with PCB exposure in workers. Elevated triglycerides were associated with serum PCB levels in some studies, and it has been suggested that PCBs alter lipid metabolism. However, studies of the distribution of PCBs indicate a greater solubility of PCBs in serum with a higher lipid content. As a consequence, elevated triglycerides cause a greater percentage of an individual's PCB body burden to appear in the blood. The association between serum PCB levels and triglycerides therefore results from triglycerides influencing serum PCB levels rather than the reverse. In conclusion, chronic exposure to PCBs in the occupational setting does not appear to produce any significant adverse human health effect other than dermatologic lesions.

4.4.3 Description of Studies of Environmentally-Exposed Persons

In addition to measuring tissue levels and daily intakes in the general population, several studies have attempted to identify health problems associated with higher-than-normal PCB exposures, most of which are related to local fish contamination problems. Under the sponsorship of the FDA, the Michigan Department of Public Health conducted a study of 182 adults consuming fish from the Great Lakes area, 105 of whom ingested more than 26 pounds of fish each year (Humphrey, 1980). The mean blood PCB concentration was 73 ppb for those who consumed more than 26 pounds of sport fish from Lake Michigan compared to only 20 ppb for individuals consuming six pounds or less, and 17 ppb for those who consumed no fish. Evaluations of health histories and current medical examinations failed to identify any differences between the exposed and control groups. No symptoms characteristic of Yusho were observed in the exposed group, and no consistent pattern of complaints or problems was identified. In a recent examination of Michigan residents with high levels of polybrominated biphenyls as well as PCBs, a similar lack of correlation between serum levels and clinical chemistry tests was reported (Kreiss et al., 1982).

A study has also been performed in residents of Triana, Alabama, an area of higher-than-normal PCB and DDT contamination (Kreiss et al., 1981). Of 458 residents with serum PCB levels ranging from 3 to 158 ppb, none of the following indices of health were associated with PCB levels: weight loss, prevalence of disease, use of medications or medical care, miscarriage, stillbirth, infant death or heart disease. There was an association between diastolic blood pressure and log PCB concentrations, but the authors failed to provide the magnitude of the change. They did state, however, that the latter observation was small and of borderline statistical significance, leaving the consequences of this association open to speculation. Interestingly, the authors of this study reported that the strongest correlation was between log DDT and log PCB serum levels, a fact which further undermines their ability to attribute a significant finding solely to PCBs. This conclusion is apparently shared by Kreiss, who in a review article later stated (Kreiss, 1985):

The Triana study results have introduced the hypothesis that PCBs may be related to blood pressure measurements. As dependent variables, both systolic and diastolic blood pressure measurements were predicted by PCB levels when controlled for major confounders including age, sex, body mass index, and socioeconomic class. ... However, the collinearity of DDT and PCB serum concentrations in this rural population, exposed to both chemical families through consumption of contaminated fish, precludes any certainty regarding which family of chlorinated hydrocarbons may be correlated with blood pressure.

Baker et al. (1980) reported a study of residents and workers in Bloomington, Indiana, examined after it was discovered that PCBs had been discharged into the municipal sewage system by a local capacitor manufacturing plant. Environmental testing in August of 1976 had found significant PCB contamination in a number of places. The mean PCB concentrations were 479 ppm in sewage sludge, 17 ppm in treated soil, and 0.15 ppm in the vegetables grown in this soil. The mean serum PCB levels were 17.4 ppb in 89 persons listed in the study as sludge users, 75.1 ppb in workers occupationally exposed, 33.6 ppb in 19 family members of the workers, and 24.4 ppb in 22 community residents with no known exposure to PCBs. The only correlation observed was between serum triglyceride levels and serum PCB levels. Chloracne and systemic symptoms were not noted in any of the exposure groups and no significant correlations were found between PCB blood levels and tests for hematologic, hepatic, and renal function.

Stark et al. (1986) examined 52 individuals (firemen, police, building personnel, and public utility employees) potentially exposed to PCBs while responding to a transformer malfunction. Apparently no fire occurred after the explosion, and polychlorinated dibenzofurans were not an issue in this incident. Blood chemistries, past medical histories, symptoms and fasting blood PCB levels were collected and compared to a control group of 68 "non-exposed" persons (mean blood levels are provided in section 4.1.4). Six weeks later all tests except blood PCB levels and CBC were repeated. The laboratory results were reported to be unremarkable, no serious clinical symptoms were observed, and only a transient skin irritation was believed to be associated with PCB exposure. When the authors controlled for age and alcohol consumption, as might be expected only plasma triglyceride levels were positively correlated to blood PCB levels. The authors of

this paper also made several additional speculations regarding blood potassium and phosphorus levels, but provided little in the way of hard data to support these claims. In fact, the article, like many of its kind, provides almost no meaningful data. For example, in Table 3 the authors report that the laboratory results of the exposed group differed significantly from that of the nonexposed group in red blood cell count, hemoglobin, hematocrit, and phosphorus. The only parameter that did not differ between groups was their blood PCB levels. None of the reported "significant" changes were clinically significant or relevant, and this table only serves to illustrate that occasionally meaningless but statistically significant differences may be found in populations with normal clinical values. Last, it should be noted that the reported PCB air concentrations in this building ranged from 0.3-1.7 $\mu g/m^3$ while the ambient air quality standard for the State of New York is 1.7 $\mu g/m^3$. In contrast, the level of trichlorobenzene was 9.5 $\mu g/ m^3$. Thus, the authors failed to control for the presence of a second chemical, and did not attempt to identify any correlations between the reported results and blood trichlorobenzene levels even though the "exposed" population clearly received greater exposure to this chemical than to PCBs.

Stehr-Green et al. (1986b) reported the results of a cross-sectional study performed in 1983 on 106 persons who had resided within 0.5 miles of a chemical waste site for a period of at least five years. Blood samples were collected for a clinical chemistry profile and PCB blood levels. The authors reported finding suggestive evidence that blood PCB levels were correlated with the occurrence of hypertension. However, this association disappeared when potentially confounding factors such as age and smoking were controlled for. The authors also reported initially finding a few other correlations, like an inverse correlation between blood PCBs and SGOT levels, but these correlations were either considered biologically implausible or were findings that could not be corroborated in further analyses. Essentially no evidence of adverse health effects was found in this study, and the authors cautioned that further evaluations would be necessary before any final conclusions could be reached.

The Greater New Bedford Health Effects Study (MDPH, 1987) was undertaken beginning in 1981 to determine the prevalence of PCB exposure and possible related health effects of residents of the New Bedford, Massachusetts area. In the

late 1970's PCBs were found to be present in the New Bedford Harbor and the Acushnet River Estuary. Phase I of the health effects study was designed to determine the prevalence of elevated serum PCB levels in residents of Greater New Bedford and to determine whether or not serum PCB levels were associated with the level of systolic and diastolic blood pressure. An elevated serum PCB level was defined as ≥30 ppb. Only 1.2% of the 322 participating residents of Greater New Bedford had elevated serum levels (≥ 30 ppb), and blood pressure measurements did not correlate with serum PCB level. A positive correlation between serum PCB level and consumption of locally-caught fish appeared to exist from the prevalence study. Consequently, an Enrichment Study involving individuals with presumed exposure to local seafood (and possibly sustaining greater PCB exposure) was undertaken in an attempt to identify a group with elevated serum PCB levels. Serum PCB levels of this group were, however, also within the typical range of the U. S. population.

The conclusions to be drawn from this study are: 1) that the general population of Greater New Bedford does not have elevated serum PCB levels, 2) that residents with the highest risk for exposure do not have elevated serum PCB levels, and 3) that low to moderate serum PCB levels are not associated with elevated blood pressure.

4.4.4 Summary of Studies of Environmentally-Exposed Persons

Several studies have sought to evaluate the health of individuals exposed to PCBs from specific environmental sources. In none of these studies was actual exposure to PCBs found to exceed that which has occurred in the occupational setting, and in general the body burdens of PCBs in the participants in these studies were far less than those of PCB-exposed workers. The evidence provided by these studies suggests that environmental exposure to PCBs has no adverse effects on liver function, lipid metabolism, or blood pressure, nor does it result in the appearance of any identifiable clinical disorder or disease. Some of these studies clearly reinforce the need to carefully evaluate whether postulated exposure pathways are complete because their populations at risk of PCB exposure have failed to provide any evidence that exposure has occurred.

4.5 MORTALITY STUDIES

4.5.1 Description of Mortality Studies

A letter to the editor in the New England Journal of Medicine in August of 1976 by Anita Bahn and colleagues at the University of Pennsylvania suggested that Aroclor 1254 was *"a possible new carcinogenic hazard"* (Bahn et al. 1976). This was based on 2 cases of malignant melanoma among 31 persons *"believed to be heavily exposed to this agent;"* in a subsequent letter one additional melanoma was reported in one of 41 refinery workers at this plant believed to have a lesser PCB exposure than that of the 31 persons working in research and development (Bahn et al., 1977).

The first Bahn letter was followed by a letter in the same journal five months later from an official of the New York State Department of Health, who stated,

> *The letter of Bahn et al. ... fails to address the very important issue of exposure to other, perhaps carcinogenic compounds. The authors list 11 different industrial uses of PCB, but do not specify in which use the study cohort was exposed. In its most common use as an impregnation fluid in capacitors and transformers, a scavenger additive is necessary to prolong the life of the device. Van Duren et al. have shown some of the epoxides that are frequently used for this purpose have carcinogenic effects. One of these, epoxide 206, a particularly effective scavenger, was found to have a 'pronounced carcinogenic effect' in an animal skin-painting experiment. In the capacitor manufacturing plant that we are now studying, epoxides have normally been added as only 0.5 percent of the PCB. However, they have a vapor pressure about 1,000 times greater than PCB. Thus, the breathing zone may contain as much epoxides as PCB (or more).*

He further states, *"It is impossible to draw any inferences from the Bahn study concerning adverse effects of PCB without information on other chemicals to which the group may have been exposed."* (Lawrence, 1977).

As is the custom, this was followed by a brief reply by Bahn and coworkers in which they indicate that *"... the extent of exposure of the workers to other*

chemicals was not known." They additionally state, *"Since we knew the R & D workers were also exposed to other chemicals which might be carcinogenic we did not emphasize the four other cancers (in three persons) reported to have occurred in the first cohort. This group includes two cancers of the pancreas which has previously been reported as associated with chemical workers."* Although Bahn et al. then reiterate their concerns for the melanomas observed in their cohort, i.e., the fact that *"early detection of this cancer may affect survival warranted in our opinion a preliminary report of its possible association with PCB,"* they conclude with the following statement, *"We agree, however, that further information is essential."*

To summarize, this preliminary study reported eight cancers which developed between 1957 and 1975 among 92 employees working at a petroleum refinery. Of the 92 total persons in this cohort, 51 were apparently employed in research and development (but only 31 were considered to be heavily exposed to PCBs), and 41 were reported to be refinery workers. The level of exposure to Aroclor 1254 was not provided or discussed, and the duration of the PCB use at the plant was only nine years (Bahn et al., 1976). Of the eight cancers reported, three were malignant melanomas and two were cancers of the pancreas. According to NIOSH (1977), *"This is significantly more skin cancer (melanoma) and pancreatic cancer than would be expected in a population of this size, based on the Third National Cancer Survey."* However, it is impossible to draw any conclusions from this study. As already stated, Lawrence (1977), of the New York State Department of Health, has criticized the authors of this preliminary report for failing to identify other chemicals to which these refinery workers and research chemists might have been exposed, some of which may easily have been skin carcinogens. A number of chemicals common to the air around petroleum refineries, e.g. benzene, are known to be human or animal carcinogens. Strangely, Bahn and coworkers recognized that the R & D personnel were also exposed to other chemicals that might be carcinogenic, but failed to consider the possible role these carcinogens might have played in the melanomas they reported. In response to the criticism of Lawrence (1977), Bahn et al. (1977) did agree that further information was essential, and apparently withdrew this study for revision. Yet in the ensuing twelve years no further

report by any of the authors of the "Bahn" letters, or of the cohort of workers studied, has appeared in the PCB literature. Given the serious limitations of this small study, it is perhaps not surprising that malignant melanomas have not been an issue in any of the epidemiologic studies of PCB-exposed capacitor workers that have been published to date.

Zack and Musch (1979) reported a small historical prospective mortality and morbidity study of workers exposed to PCBs at one of the Monsanto manufacturing plants located in Sauget, Illinois. This report remains unpublished but is of interest because the number of deaths examined approximates that examined in more recent studies by Bertazzi et al. (1987) and Gustavsson et al. (1986). PCBs were manufactured at this plant from 1936 to 1977. All employees who had worked in the PCB department for at least six months, between January 1, 1945 to December 31, 1965, were selected for this study. During this period of time the process by which PCBs were manufactured remained relatively constant. It basically consisted of batch chlorination of biphenyl in the presence of iron and iron chloride catalysts. Through interviews of plant personnel, the authors determined that PCB exposure levels did not vary much within the PCB department. Other chemical exposures in this department included hydrochloric acid, tri- and tetrachlorobenzene, biphenyl and chlorine gas. The exposed worker cohort was identified from the plant's computerized work history system, and 89 employees met the criteria for inclusion in this study. Of the eighty-nine members of the cohort, 30 were verified as deceased by death certificate and 58 were verified to be living. Thus, the vital status was ascertained for 99% of the cohort as of December 31, 1977. The underlying cause of death was coded to the 8th revision of the International Classification of Disease, Adapted for Use in the United States by an experienced nosologist. The mortality comparisons were made to the general U. S. population.

A total 1,800 person-years of experience were observed for this population. Most of the subjects were persons 35-60 years of age, who accounted for 74% of the total. The average length of exposure for the living members of the cohort was 3.2 years while that of the deceased group was 3.7 years. Although the total number of deaths showed a less than two-fold excess of malignant neoplasms

and a greater than two-fold excess in deaths from cardiovascular disease, the only statistically significant increase in mortality was for diseases of the circulatory system (see Tables 4.5.1 and 4.5.2). As can be seen from Table 4.5.2, the non-significant excess of malignant neoplasms reported for the cohort was

Table 4.5.1

Total Mortality by Category for the Zack and Musch Study

I.C.D.	Cause of Death	Observed/Expected	SMR
	All causes	30/22.88	131
140-209	All malignant neoplasms	8/4.46	179
140-149	Buccal cavity/pharynx	0/0.16	0
150-159	GI tract/peritoneum	1/1.33	75
155,156	Liver	0/0.10	0
-- --	All other digestive organs	1/1.23	81
162,163	Lung	4/1.44	278
185-189	Urinary tract	1/0.51	196
200-209	Lymphatic/hematopoietic	1/0.40	250
-- --	Other sites	1/0.53	189
390-458	Diseases- circulatory system	16/11.17	143
410-413	Atherosclerotic	7/7.19	97
----	All others	9/3.98	* 226
460-519	Diseases of the respiratory system	1/1.27	79
520-577	Diseases of the digestive system	2/1.20	167
----	All other diseases	2/2.40	83
	External causes of death	1/2.38	42

* $p < 0.05$; number of persons observed = 89

Adapted from Zack and Musch (1979)

Table 4.5.2

A. Mortality by Category for White Males

I.C.D.	Cause of Death	Observed/Expected	SMR
	All causes	18/13.53	133
140-209	All malignant neoplasms	4/2.70	148
150-159	GI tract/peritoneum	0/0.75	0
155,156	Liver	0/0.05	0
-- --	All other digestive organs	0/0.70	0
162,163	Lung	3/0.89	337
185-189	Urinary tract	0/0.28	0
200-209	Lymphatic/hematopoietic	0/0.28	0
-- --	Other sites	1/0.36	278
390-458	Diseases- circulatory system	11/6.82	161
410-413	Atherosclerotic	4/4.99	80
----	All others	7/1.83	526*
460-519	Diseases of the respiratory system	0/0.73	0
520-577	Diseases of the digestive system	1/0.75	133
----	All other diseases	2/1.10	182
	External causes of death	0/1.43	0

B. Mortality by Category for Nonwhite Males

I.C.D.	Cause of Death	Observed/Expected	SMR
	All causes	12/9.35	128
140-209	All malignant neoplasms	4/1.76	227
150-159	GI tract/peritoneum	1/0.58	172
155,156	Liver	0/0.05	0
-- --	All other digestive organs	1/0.53	189
162,163	Lung	1/0.55	182
185-189	Urinary tract	1/0.23	435
200-209	Lymphatic/hematopoietic	1/0.12	833
390-458	Diseases- circulatory system	5/4.35	115
410-413	Atherosclerotic	3/2.20	136
----	All others	2/2.15	93
460-519	Diseases of the respiratory system	1/0.54	185
520-577	Diseases of the digestive system	1/0.45	222
----	All other diseases	0/1.30	0
	External causes of death	1/0.95	105

* $p < 0.05$;
Adapted from Zack and Musch (1979)

due primarily to an increase in lung cancer in the white male population, accounting for three of the four cancers in this group. A similar increase was not observed in non-white males, and in neither group was the difference between the observed and expected incidence statistically significant. The identities of the 8 specific cancers observed in this cohort are as follows: 1 carcinoma of the colon, 2 carcinomatosis (one of the kidney), 4 carcinomas of the lung, and 1 multiple myeloma. Given the fact that the significant increase in cardiovascular disease was race specific, and that the smoking histories of the members of this cohort were not examined, the significance of this single uncorroborated finding cannot be determined. The authors of this study reached the following conclusions:

> *The results of this study do not corroborate an excess risk of pancreatic cancer or malignant melanoma among workers exposed to PCBs as reported in the study of Mobil workers (Bahn et al., 1977). Nor do the results uphold translating to man the outcome of animal tests, in which hepatomas have been associated with long-term exposure. In this study, no deaths were observed from pancreatic or liver cancer or malignant melanoma.*
>
> *The SMR for all causes was elevated from what one would expect in an industrial cohort. The high SMR for white males is, for the most part, explained by the excess in deaths from circulatory diseases exclusive of arteriosclerotic heart diseases. This cause-of-death category includes deaths from rheumatic heart disease, cerebrovascular disease, and other forms of heart disease, all of which are unlikely to be related to exposure in the workplace. It is urged that a larger study be undertaken of the total Krummrich plant population to evaluate the overall risk of death from all causes and from cardiovascular diseases.*

Bertazzi et al. (1981) reported the results of a mortality study of workers employed at a capacitor manufacturing facility located just north of Milan, Italy. This facility had been manufacturing large power capacitors impregnated with PCB dielectric fluids since 1946. From 1946-1964 the PCB fluids used at this plant were commercial mixtures containing 54% chlorine, i.e. Aroclor 1254 and Pyralene 1476. Starting in 1965 these fluids were progressively replaced by mixtures of 42% chlorine content, primarily Pyralene 3010 and 3011, and by 1970 these latter products were the only ones in use. Although no reliable data were available detailing the magnitude of past

exposures, three cases of chloracne had been reported in 1954. These cases had developed in three young autoclave workers some 4-7 months after their work in this area had begun. Air samples collected in their area of the plant were reported to contain PCB concentrations of 5.2, 6.4 and 6.9 mg/m^3. These results clearly exceeded the air standards of 1.0 and 0.5 mg/m^3 later developed for PCB mixtures of 42% and 54% chlorine, respectively. The results of an industrial hygiene survey performed at this plant in 1977 also provide some insight as to the level of PCB exposure experienced by the workers of this plant, and the values cited appear to be those reported by Maroni et al. (1981a). That is, nine TWA area air samples ranged from 48-275 $\mu g/m^3$, 18 surface samples ranged from 0.2-159 $\mu g/cm^2$, and the skin wipes of 9 workers ranged from 0.3-9.2 $\mu g/cm^2$.

The cohort studied consisted of all male and female workers who had accumulated at least 6 months of employment during the period of 1946 through December 31, 1970, excluding the clerical workers in administrative departments. Some 1,310 persons met this criterion, 1,020 women and 290 men. The mortality study of these workers covered a 25-year period (from 1954-1978), and the vital status of each individual was ascertained as of December 31, 1978. The vital status of the study population was reported to be 98% complete, and an estimated 20,565 person-years were accumulated by the 1,310 individuals of this cohort.

As of 1978, 27 deaths had occurred in this population. When mortality was broken down by cause of death, 14 (52%) were related to cancer while 5.65 were expected. This excess in the cancer mortality resulted primarily from an unusually high incidence of cancer in the male population, where 8 out of 12 reported deaths (67%) were cancer-related. In the female population, this ratio was 6 of 15, or 40% (not statistically significant). (See Table 4.5.3). The authors also reported higher-than-expected incidences of cancer of the digestive organs and cancer of the lymphatic or hematopoietic systems. However, these findings were not significant for either sex.

Table 4.5.3

Mortality in Italian Capacitor Workers

Cause of Death	Observed	Expected	SMR
	Males		
All causes	12	12.72	94
All neoplasms	8	3.32	241*
digestive organs and peritoneum	3	0.88	340
lymphatic and hematopoietic	2	0.46	435
Accidents, etc.	3	2.56	117
	Females		
All causes	15	7.72	194*
All neoplasms	6	2.23	253
lymphatic and hematopoietic	2	0.45	444
Accidents, etc.	5	2.23	224

* $p<0.05$

Adapted from Bertazzi et al. (1981)

The data provided by Bertazzi et al. (1981) are not particularly descriptive as most cancers have been lumped into one of two major categories for the male population and only one category for the female population. It is notable, however, that no liver or skin cancers were reported for this cohort, even though the digestive sites did include the biliary tract.

In 1987 Bertazzi et al. published an update of their study. In this second report, the cohort had been modified to include non-production workers at the plant; the minimum period of employment was reduced from six months to one week; and mortality was followed through 1982. The vital status of employees was determined for over 99% of the population. These changes increased the size of the cohort to 2,100 total employees (544 males and 1,556 females), the number of person-years to 41,010, and the number of deaths to 64. The results for male and female workers, which were analyzed separately, are summarized in Tables 4.5.4 and 4.5.5. As in their prior report, the excess mortality from cancer in the male population was statistically significant. Of the primary sites identified, the observed incidence of neoplasms of the GI tract now exceeded the level of statistical significance. The incidences of lung and hematologic neoplasms were also greater than expected, but neither increase was statistically significant. In spite of these elevations, the mortality for all causes was at the expected level. Among females, higher-than-expected incidences were observed in total mortality for all causes, mortality from cancer, and in the incidence of hematologic neoplasms, when compared to the local mortality rates. In the total cohort, there was one case of liver cancer, occurring in a person with limited PCB exposure, and there were no cases of rectal cancer.

Even though the authors point out that any interpretation of their results is limited by the small number of deaths that have occurred to date in their cohort and also state that their results *"did not permit a causal association to be either proved or dismissed,"* they nevertheless suggest that their study supports the possibility that PCBs pose a carcinogenic risk to humans. Even putting aside the small number of deaths, their study results do not support this suggestion.

Table 4.5.4

A. Mortality from Selected Causes of Male Workers Exposed to PCB

Cause of death	Reference Cohort: National Observed	National Expected	National SMR	Local Expected	Local SMR
All causes	30	27.8	108	29.8	101
Malignant tumors	14	5.5	253[a]	7.6	183[b]
Cancer of G.I. tract	6	1.7	346[c]	2.2	274[d]
Lung cancer	3	1.2	250	1.6	187
Hematologic neoplasms	3	0.8	375	1.1	263
Cardiovascular disease	8	7.9	101	9.4	95
Accidents	6	6.8	88	5.8	103
Confidence limits (95%)	[a]= 144-415 [c]= 141-721 [b]= 104-300 [d]= 112-572				

B. Mortality from Selected Causes of Female Workers Exposed to PCB

Cause of death	Reference Cohort: National Observed	National Expected	National SMR	Local Expected	Local SMR
All causes	34	25.8	132	16.5	206[a]
Malignant tumors	12	7.7	156	5.3	226[b]
Hematologic neoplasms	4	1.5	266	1.1	377[c]
Cardiovascular disease	2	4.7	42	3.0	66
Accidents	9	4.0	225	4.0	225
Confidence limits (95%)	[a]= 145-285 [c]= 115-877 [b]= 123-385				

Adapted from Bertazzi et al. (1987)

Table 4.5.5

A. Characteristics of Selected Cases of Cancer Deaths Among Male Workers Exposed to PCBs

Cancer type/site (ICD 8th revision)	Age at hire(yr)	Year of hire	Length of exposure(yr)	Latency (yr)	Age at death(yr)
Stomach (151)	**59**	**1948**	**.4**	**7**	**66**
Stomach (151)	**49**	**1951**	**17.2***	**23**	**72**
Liver (155)	**33**	**1957**	**.3**	**17**	**50**
Biliary tract (156)	**41**	**1959**	**1.0**	**14**	**55**
Pancreas (157)	**53**	**1969**	**5.8***	**5**	**58**
Pancreas (157)	35	1960	21.7	22	57
Lung (162)	**60**	**1951**	**6.7**	**26**	**86**
Lung (162)	**28**	**1954**	**.1**	**7**	**35**
Lung (162)	**38**	**1962**	**.5**	**19**	**57**
Reticulum cell sarcoma (200)	27	1952	7.0	15	42
Acute myelocytic leukemia (205)	21	1961	19.0	19	40
Acute hemocytoblastic (205)	32	1967	2.2	2	34

B. Characteristics of Selected Cases of Cancer Deaths Among Female Workers Exposed to PCBs

Cancer type/site (ICD 8th revision)	Age at hire(yr)	Year of hire	Length of exposure(yr)	Latency (yr)	Age at death(yr)
Hodgkins disease (201)	20	1960	21.8	22	42
Hodgkins disease (201)	19	1949	12.2	15	34
Hodgkins disease (201)	**17**	**1960**	**0.2**	**0.2**	**18**
Lymphosarcoma (200)	**24**	**1968**	**0.7**	**2**	**26**

Adapted from Bertazzi et al. (1987)
* Worked as a plant guard
(Note: All cancers reported in persons hired at advanced age (age 59 or older) or in persons with a length of PCB exposure ≤ 1 year, or persons believed to have had little known exposure to PCBs (e.g. a plant guard) have been highlighted as potentially spurious findings).

First, there was no association between duration of exposure, latency, or year of first exposure for any of the causes of mortality. This is in direct contrast to what one would expect to find if a chemical were actually carcinogenic.

Second, the fact that excess cancer was observed when the cohort was enlarged to include administrative personnel and others only minimally or not exposed to PCBs suggests that PCB exposure was not the causal factor in these cancers. The authors themselves state:

> *However, interpretation of such a result is limited by an examination of individual cancer cases; of the two workers dying from stomach cancer, one had been hired at an advanced age and had experienced a very short exposure, and the other one was a plant guard not involved in production processes; both workers who died from cancer of the liver and biliary tract had been employed in the production area, albeit for rather short periods. The cases of pancreatic cancer occurred in another plant guard (no direct exposure reported) and in a worker who had been exposed directly in the process area for over 20 years. Given this information, no clear cut and definite conclusion regarding the association between cancer of the GI tract and exposure to PCBs can be drawn from the results of the study.*

If one subtracts from the reported mortality those persons either not exposed (two guards) or minimally-exposed (i.e. ≤ 4 months), the ratio for the number of observed cancer deaths of the GI tract in males versus the expected number of deaths drops to 2/2.2 for an SMR of 91 when compared to the local mortality rates. If the definition of minimally-exposed were a year or less, the ratio of observed to expected becomes 1/2.2 for an SMR of only 45.

Similarly, the reported significant increase in hematologic cancers in women disappears if one removes the two persons minimally exposed, i.e. those with 0.2 and 0.7 years of exposure. This change seems particularly justified as the two women with minimal exposure also are the two persons for whom the latency period was reported to be 0.2-2 years. Removing these cases reduces the SMR to either 182 or 133 (2/1.1 or 2/1.5) depending upon which reference mortality is used, and neither comparison would be statistically significant. In addition to those cancers which were reported to be significantly elevated in either sex, it is apparent that of the three lung cancers observed, one occurred in

a person first employed at age 60, and the other two represent persons with exposures of very short duration, i.e. 1-6 months.

If the above information is taken into consideration, and all cancers not likely to be related to the men's work history are subtracted, the total number of cancers observed in men is reduced to six. The SMR then becomes 109 or 79, depending upon which reference cohort the data are compared to. Thus, it does not appear that any of the *"significant"* associations reported by Bertazzi et al. (1981) are likely to be the result of PCB exposure.

An additional problem with the results of this study is the fact that the apparent associations are sex-specific. In males, only cancers of the GI tract are said to be significantly elevated. This category, actually a combination of several different types of cancer, was not elevated in women. Conversely, the types of hematological cancers that were reported as significantly elevated in women (Hodgkins disease and lymphosarcoma) were not observed at all in the male population.

A further problem with this study is the fact that other confounding contributors to mortality have not been identified and controlled for in this study. For example, in the female population, both "all causes of death" and "death by accidents" are significantly elevated. The latter elevation affects the overall death rate, but cannot be attributed to PCBs. Another confounder is the fact that an excess of leukemia is common to jobs with exposures to electromagnetic fields. As the authors note, this phenomenon may have contributed to the excess hematologic neoplasms observed in women.

Also, nowhere is it explained why local mortality rates from cancer are 45% lower than the national rates in females and 38% higher in males. One must question both the magnitude of the disparity and the inconsistency between the sexes concerning the local and national rates which makes interpretation of the data most difficult.

Given the above limitations of the Bertazzi studies, it would appear that the associations put forth in these studies are tenuous at best. The authors

themselves questioned the basis of the cause of cancer mortality, stating, *"The elevated cancer mortality (in women) might be interpreted, in our view, in the light of some peculiar occupational factor in addition to the already named social factors."* As the authors recognized, the substantial number of problems inherent in the Bertazzi studies preclude a conclusion that there is a causal association between PCBs and cancer of any kind.

Brown and Jones (1981) conducted a retrospective mortality study of 2,567 employees from two plants where PCBs were used to manufacture electrical capacitors. These plants were selected for study for the following reasons: a) each had a large work force, b) PCBs had been used for more than 30 years, c) there was considerable exposure to PCBs, and d) the workers' records were readily available. At the time of the study both plants were still using PCBs. Plant No. 1, located in New York, was actually two facilities, one which had made small industrial capacitors since 1946 and a second facility that had made large power capacitors since 1951. Plant No. 2 was located in Massachusetts and had manufactured PCB-containing capacitors since 1938. Both plants used similar manufacturing procedures, including a trichloroethylene wash, and both had used several different PCB fluids.

All workers included in the study were employed for at least three months in areas of PCB exposure, but if the work history indicated an employee had potential exposure to trichloroethylene, that employee was excluded from the cohort. The vital status of 98% of the population was determined and 39,018 person-years were accumulated. (See Table 4.5.6). The remaining 2% (55 persons) of the cohort for which the vital status was unknown were assumed to be alive as of January 1, 1976 for the purposes of analysis. The study period was from 1940 until the first day of 1976.

An industrial hygiene survey was performed at both plants in the spring of 1977, or approximately one year after the end of the study period. In Plant No. 1, the TWA for personal samples ranged from 24-393 $\mu g/m^3$ and for area samples from 3-476 $\mu g/m^3$. In Plant No. 2, these measurements ranged from 170-1260

Table 4.5.6

Vital Status and Duration of Employment of the Brown and Jones Cohort

	Plant #1			Plant #2			Grand Total
	Males	Females	Total	Males	Females	Total	
A. Vital Status of Cohort							
Known to be alive	520	360	880	633	836	1,469	2,439
Known to be deceased	55	18	73	28	62	90	163
Unknown vital status	8	7	15	14	26	40	55
Total	583	385	968	675	924	1,599	2,567
Person-years	7,825	5,185	13,010	9,229	16,779	26,008	39,018
B. Duration of Employment of Cohort							
3-6 months	137	79	216	211	207	418	634
0.5-1 year	88	59	147	127	161	288	435
1-2 years	93	92	185	118	175	293	478
2-3 years	53	41	94	64	82	146	240
3-10 years	165	82	247	123	188	311	558
10 years	47	32	79	32	111	143	222
Total	583	385	968	675	924	1599	2,567

Adapted from Brown and Jones (1981)

$\mu g/m^3$ for personal air samples and from 50-810 $\mu g/m^3$ for area samples. Although these data suggest exposure was greater in Plant No. 2 at the time of the survey, the historic exposures may have been more equivalent. Furthermore, Plant No. 1 had used several different stabilizers (< 1%) since the 1960's, including two potentially carcinogenic epoxides.

The data concerning the major causes of death for the 163 persons who had died during the interval studied are displayed in Table 4.5.7. The overall mortality and the mortality from each of the major causes of death were less than expected, although not to a statistically significant degree. For the cohort there were no statistically significant excesses observed for cancer of any kind. The rectal cancer rate in the female population of Plant No. 2 was reported to be higher than expected (3 observed, 0.5 expected), but no rectal cancers were observed in females at Plant No. 1, and only one was observed in the total male population of both plants. The mortality from liver cancer was elevated, but not to a statistically significant degree. There was no relationship between latency or length of exposure and the incidence of liver cancer as would be expected if a chemical exposure were the causal agent. Actually, the fact that the cancer incidence is inversely related to the duration of exposure suggests PCBs were not the causal agent.

When the total cohort was considered there was no statistically significant relationship for any cause of death. To quote the authors, the findings of this study can be summarized as follows:

> *The only categories of cancer in which the number of observed deaths are greater than expected are for cancer of the rectum and cancer of the liver and only a slight increase for breast cancer. When both cohorts are combined none of the excesses are statistically significant. ... ...*
>
> *There is no relationship between increasing durations of employment in jobs involving PCB exposure and the risk of mortality due to cancer or cirrhosis of the liver. ... ...*
>
> *When cancer mortality is examined by plant, it is evident that most of the excesses occur in plant 2 - especially among the female group. This finding may be related to more exposures to PCBs at*

Table 4.5.7

Major Causes of Death for Plant Workers Exposed to PCBs: Brown and Jones (1981)

Causes of Death	Observed/Expected	Standard Mortality Rate
	All Causes	
All malignant neoplasms	39/43.79	(89)
Diseases of nervous system	11/12.55	(88)
Diseases of circulatory system	60/62.93	(95)
Accidents	13/18.29	(71)
All other causes	40/44.79	(80)
All causes	163/182.35	(89)
	Malignant Neoplasms	
Cancer of stomach	1/1.66	(60)
Intestine	4/4.03	(99)
Rectum	4/1.19	(336)
Liver (not specified)	3/1.07	(280)
Pancreas	1/1.90	(53)
Respiratory	7/7.98	(88)
Breast	7/6.84	(102)
Lymphatic	2/4.34	(46)
Other	10/14.78	(68)
Cirrhosis	6/5.6	(107)

Source: Brown and Jones (1981)

plant 2, as indicated by the industrial hygiene results. In addition, there was an opportunity for earlier exposures at plant 2, potentially allowing for a longer latency period. However, this difference in mortality may be a function of the size of the cohorts (plant 1 only has half the number of person-years as plant 2), and thus, simply be a statistical quirk. ... ...

A potential confounding variable or interaction variable in this study is the possible effect of alcohol ingestion on the observed increase (in plant 2) in mortality from cirrhosis of the liver. However, this cannot be properly assessed in the present study, since not enough is known about the ingestion of alcohol among the entire study cohort. ...

All-cause mortality is lower than expected, and there was no increase in mortality for the major causes of death.

In 1987 Brown reported the results of the first follow-up study of this population, adding seven more years of observation. The number of deaths in the cohort increased during this period from 163 to 295. Unlike the Bertazzi study, however, Brown did not alter the criteria for selecting the cohort in his update. Two findings were of particular interest. The first was the fact that no additional deaths from cancer of the rectum had occurred, reducing the difference between the observed and expected values, and indicating that the prior finding was in fact a chance observation unrelated to PCB exposure (Table 4.5.8).

The second finding of interest was the addition of two deaths attributed to cancer of the liver or biliary passages in females from Plant No. 2. When taken alone, the observed five cancers of the liver and biliary tract represent a statistically significant increase over the expected 1.9 cancer deaths for these tumor sites. However, the cohort used by Brown is the only one to date for which an increased incidence of liver neoplasms has been reported or even suggested. Also, close examination of the liver/biliary cancer deaths indicates that only one of these deaths was attributable to primary hepatic carcinoma (Table 4.5.9). Of the remaining liver carcinomas, one was the apparent result of metastasis from another site, and the origin of a second cancer has not yet been confirmed. Thus, the origin of two of the five liver/biliary cancers reported thus far is not clear. In addition, there was no apparent association between liver cancer

Table 4.5.8

Major Causes of Death for Plant Workers Exposed to PCBs: Brown (1987)

Causes of Death	Observed/Expected	Standard Mortality Rate
	All Causes	
All malignant neoplasms	62/79.7	(78)
Diseases of nervous system	20/22.6	(88)
Diseases of circulatory system	120/115.6	(104)
Accidents	21/25.8	(81)
All other causes	72/73.9	(97)
All causes	295/317.6	(93)
	Malignant Neoplasms	
Cancer of stomach	1/2.8	(36)
Intestine	8/7.7	(104)
Rectum	4/1.9	(211)
Liver	5/1.9*	(263)*
Pancreas	2/3.7	(54)
Respiratory	10/16.9	(59)
Urinary	4/2.8	(143)
Hematopoietic	5/7.4	(68)
Breast	9/11.7	(77)

* $p < 0.05$

Adapted from Brown (1987)

Table 4.5.9

Description of Liver/Biliary Passage Deaths

Length of PCB exposure	Sex	Cause of Death	Hospital/Pathology Report
1 yr	male	Primary carcinoma of liver	Confirmed as intrahepatic bile duct cancer with metastasis
1.5 yr	female	Carcinoma of the biliary system	No reports available
9.8 yr	female	Carcinoma of the gallbladder	Adenocarcinoma of liver and gallbladder. Origin probably gallbladder, metastatic to liver
0.8 yr	female	Bile duct cancer	Cancer of the bile ducts. Origin probably from bile ducts. A history of cancer of the uterus.
0.3	female	Carcinoma of the liver	Hepatic coma due to hepatoma, due to metastatic disease, primary site unknown.

Adapted from Brown (1987)

mortality and either the duration of exposure or the latency period since first exposure. For example the actual etiologic agent of most of the liver cancers listed in Table 4.5.9 is not clear. One is reported to have occurred after only 0.3 years of exposure, and 4 of the reported 5 liver/biliary cancers occurred in persons with 1.5 years or less of significant PCB exposure (i.e., 0.3, 0.8, 1.0 and 1.5 years). Only one liver/biliary cancer was observed in a person with more than 1.5 years of PCB exposure, and this tumor is listed as having metastasized from another tissue. Thus, there is a clear and irreconcilable disparity between the length of PCB exposure and the observed occurrence of liver/biliary tumors. Also, Brown (1987) notes that the distribution of specific types of liver and biliary system cancer is similar to that expected based on mortality figures for the United States. Thus, it does not appear that the incidence of any specific type of carcinoma has been enhanced by PCB exposure. Last, and as previously mentioned in the Brown and Jones (1981) study, alcohol consumption is one confounding variable that has not been addressed in either study.

Brown himself concludes that his 1987 study provides only a limited association between PCBs and liver/biliary cancer and cites such problems as 1) a possible misclassification of some of the liver tumors, 2) the fact that the biliary and gall bladder tumors in humans differ from the type of cancer induced in animals (hepatocellular), and 3) that the pattern of risk versus latency or exposure was inconsistent with that of an occupational carcinogen, as important confounders. As discussed in the preceding paragraph, we agree with this assessment. Other than the cancer deaths in the liver/biliary category, no other striking differences were noted (see Table 4.5.8). As in the previous study by Brown and Jones (1981), mortality from all causes was lower than expected, as was mortality from all cancers (Brown, 1987).

Gustavsson et al. (1986) reported on a cohort of 142 male Swedish workers engaged in the manufacture of electrical capacitors. In this plant PCBs were used from 1960 to 1978, and the dielectric fluid was one of 42% chlorine. The cohort consisted of those persons employed for at least six months between the years 1965 and 1978, and the vital status was determined for all 142 persons included in this study. The expected number of deaths were calculated from national statistics and were standardized for sex, age-class and calendar year.

The mean exposure duration was 6.5 years, and air sampling performed in 1973 showed a level of 0.1 mg/m^3, although exposures in the 1960's may have been higher.

There were 21 deaths for this cohort while 22.12 were expected. Of these, seven were caused by cancer, an excess that was not statistically significant (5.39 expected; see Table 4.5.10). A subgroup of 19 individuals with higher exposures than the rest of the cohort, e.g. capacitor fillers and capacitor repairmen, was analyzed separately, and there was no increase in mortality or of cancer incidence in this high-exposure subgroup. While the authors note the results of their study must be tempered by its small size, they state "*the results do not indicate any excess mortality or cancer incidence in this factory ... .*"

Table 4.5.10

Mortality and Cancer Incidence in Swedish Capacitor Manufacturing Workers

Mortality	Observed/ Expected	Relative Risk	95% Confidence Interval
Total Mortality	21/22.12	0.95	0.58-1.45
Cancer	7/5.39	1.30	0.52-2.67
Circulatory disease	8/11.40	0.70	0.30-1.38
Ischemic heart disease	6/8.38	0.72	0.26-1.55
Respiratory diseases	2/0.96	2.08	0.25-7.50
Other causes	4/4.37	0.91	0.24-2.34
Total Cancer Incidence	7/7.58	0.92	0.37-1.90

Adapted from Gustavsson et al. (1986)

The last study of interest is a preliminary study issued by Nicholson et al. (1987), which like the study of Zack and Musch (1979) has not yet been published in a peer-reviewed journal. The cohort consists of 788 employees (459 males and 329 females) at two capacitor manufacturing facilities in upstate New York (one of these plants is one studied by Brown). The vital status all but eleven members of the cohort was determined as of 1982. All death certificates were obtained and the cause-specific mortality incidence was analyzed separately for male and female workers utilizing age- and calendar year-specific mortality rates of New York State (excluding New York City).

Workers were selected for the cohort if: 1) they had achieved five years of service, 2) they had begun employment prior to 1954, and 3) their last follow-up was at least ten years from the onset of their PCB exposure. At each facility, Aroclors 1254 and 1242 were used prior to 1970 while Aroclor 1016, and occasionally Aroclor 1221, were used after that time. One facility made smaller electrical capacitors while the other made primarily large industrial capacitors; however, the authors felt that the magnitude of the PCB exposures for the workers at each plant were quite similar. Industrial hygiene surveys of the workplace air were taken at each plant in 1977. These surveys indicated that certain job locations involved PCB exposures ranging from 300 to 1,000 $\mu g/m^3$. These exposure measurements were later used to categorize and compare groups of workers with respect to PCB exposure and cause of mortality.

The observed numbers of deaths attributed to "all causes," "all cancer," and "all cardiovascular diseases" were below the expected numbers of deaths for both males and females (Tables 4.5.11 and 4.5.12). Further, there was no excess in mortality associated with colo-rectal cancer or hepato-biliary cancer. When the cohort was divided into three equal-size groups of based on PCB exposure, no dose-related trends were identified. A comparison of individual mortality experience by job location within each plant revealed that one of the plants (small capacitor) showed a slightly increased lung cancer rate. However, the smoking habits of this cohort were not controlled for, and no statistical significance was attributed to this finding. At the same plant, the occurrence of all six observed leukemias or lymphomas was significantly ($p < 0.05$) elevated compared to 1.83 expected, but the overall incidence of leukemia and lymphoma

TABLE 4.5.11

MORTALITY AMONG FEMALE PCB WORKERS 10 OR MORE YEARS AFTER ONSET OF EXPOSURE
(By years from onset of PCB exposure)

	Total			10-19			20-29			30-39		
	Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
ALL CAUSES	51	60.16	85	10	14.05	71	24	28.04	86	17	18.07	94
CANCER, ALL SITES	19	20.28	94	3	5.05	59	12	9.67	124	4	5.56	72
Lung cancer	4	2.57	---	0	0.38	---	2	1.31	---	2	0.88	---
Colo-rectal cancer	2	2.87	---	1	0.65	---	0	1.36	---	1	0.86	---
Female breast cancer	5	5.05	99	0	1.47	---	5	2.40	208	0	1.18	---
Leukemia, lumphomas	3	1.55	---	1	0.39	---	1	0.72	---	1	0.44	---
Other	5	8.24	---	1	2.16	---	4	3.88	---	0	2.20	---
CARDIOVASCULAR DISEASES	16	26.51	60	1	5.23	19	8	12.30	65	7	8.98	78
Heart diseases	11	19.91	55	1	3.81	---	6	9.27	65	4	6.83	59
Cerebrovascular lesions	2	4.88	---	0	1.05	---	2	2.22	---	0	1.61	---
Other circulatory	3	1.72	---	0	0.37	---	0	0.81	---	3	0.54	---
CIRRHOSIS OF LIVER	2	1.61	---	0	0.51	---	2	0.78	---	0	0.32	---

SMR's are estimated for cells with five or more deaths.

Adapted from Nicholson et al. (1987)

TABLE 4.5.12

MORTALITY AMONG MALE PCB WORKERS 10 OR MORE YEARS FROM ONSET OF EXPOSURE
(By years from onset of PCB exposure)

	Total			10-19			20-29			30-39		
	Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
ALL CAUSES	137	150.06	91	44	42.27	104	67	74.43	90	26	33.36	78
CANCER, ALL SITES	25	35.08	71	8	8.75	91	17	18.04	94	0	8.29	---
Lung cancer	10	11.70	85	4	2.72	---	6	6.20	97	0	2.78	---
Colo-rectal cancer	5	5.04	99	2	1.23	---	3	2.57	---	0	1.24	---
Leukemia, lymphomas	3	3.04	---	1	0.92	---	2	1.48	---	0	0.64	---
Other cancer	7	15.30	46	1	3.88	---	6	7.79	77	0	3.63	---
CARDIOVASCULAR DISEASES	77	82.11	94	22	22.86	96	39	40.82	96	16	18.43	87
Heart diseases	67	68.19	98	16	19.42	96	35	33.82	103	16	14.95	107
Cerebrovascular lesions	3	9.04	33	2	2.25	---	1	4.50	---	0	2.29	---
Other circulatory	7	4.88	143	4	1.19	---	3	2.50	---	0	1.19	---
CIRRHOSIS OF LIVER	4	3.86	---	2	1.35	---	1	1.91	---	1	0.60	---

SMR's are estimated for cells with 5 or more deaths.
Adapted from Nicholson et al. (1987)

of the total cohort was only slightly elevated and was not significant. The authors concluded that this finding had no biological significance because the PCB exposures at each plant were not thought to differ substantially and because the overall increase observed in this category was small.

In contrast to other PCB-worker mortality studies, Nicholson et al. (1987) carefully selected their cohort based on a substantial PCB exposure (i.e., duration of > 5 years) and latency period (>10 years), two factors which would be expected to skew the results in favor of finding any chemically-induced excess in cancer. It is therefore of interest that Nicholson et al. conclude the following, *"The overall results of this analysis do not indicate any association of PCB exposure with excess mortality for any cause."*

While the preceding studies provide the most definitive data regarding the human carcinogenicity of PCBs, one additional study, although preliminary in nature, is relevant. Dr. Hamilton of General Electric has released a letter describing the preliminary results of a case-control study underway as of this writing. The study consists of an examination of all male employees of the General Electric facilities in Pittsfield, Massachusetts who died between 1969 and 1984 with a view to comparing the *"cancer mortality among workers exposed to certain chemicals with the cancer mortality among workers not exposed to those chemicals."* The substances of concern are PCBs, TCE, benzene, cutting oils, and solvents, among others.

Neither the size of the cohort nor the specific data is presented in the brief preliminary report. The statement is made however, that preliminary analysis of the data indicates that the overall cancer experience is normal for a worker population and that the rate among workers exposed to particular chemicals was not greater than the rate among workers not exposed to those chemicals. The specific types of cancers that had prompted the study do not appear to have occurred at elevated rates among workers exposed to particular chemicals. The author also states that *"further work is planned to seek more conclusive results as soon as possible."* These results obviously will be awaited with interest.

4.5.2 Summary of Mortality Studies

The data resulting from the mortality studies performed to date have not provided evidence of carcinogenicity in humans from exposure to PCBs. Most of the studies are negative on this point. In each of the studies where positive associations between PCBs and carcinogenicity were suggested, weaknesses in the studies did not permit a causal association to be either proved or dismissed.

When the studies are considered collectively, they do not meet the epidemiologic criteria necessary to establish a causal relationship between PCBs and cancer of any kind. The criteria used in making this determination are: 1) strength of the association (is the association substantial or marginal?); 2) consistency of effect (is the same type of cancer uniformly observed in a number of studies?); 3) temporal relationships (is there a plausible relationship between latency and cancer incidence?); 4) dose-response relationships (does risk of cancer increase with increasing exposure?); 5) biological plausibility (is there supporting animal evidence?); and 6) coherence of the the evidence.

The first consideration under these criteria are the strength of the association and the consistency with which it has been demonstrated. For cancer in general, the association can be considered no better than weak. Bertazzi et al. (1981;1987) reported a significant increase in overall cancer rate, but many of these cancers were contributed by individuals with questionable PCB exposure. The much larger studies of Nicholson et al. (1987) and Brown (1987) found no excess in overall cancer rate, and in fact the observed rates were slightly less than expected. Smaller studies by Zack and Musch (1979) and Gustausson et al. (1986) also found no increase in cancer rate. The purported associations between PCBs and specific cancer types were for malignant melanoma, cancers of the digestive tract, hematologic cancers, and liver/biliary cancer. Not only do the associations purported in each study differ, but significant limitations are inherent to each purported association. For example, the preliminary report of Bahn et al. (1976) which purported malignant melanomas is confounded by the fact that the cohort studied was exposed to a number of chemicals other than PCBs and the fact that this association was never confirmed in any of the larger studies that followed. Bertazzi et al. (1987)

reported a significant excess of GI tract cancers in males and of hematologic cancers in females. These findings are confounded by the fact that: 1) they have not been verified in any other study, 2) the classifications used are overly broad, 3) each association is sex specific, and 4) when persons of limited exposure are removed from the cohort both associations disappear. Similarly, the reported excess of liver/biliary tumors by Brown (1987) disappears when either tumors of questionable origin are removed or when cancers of short latency or following limited exposure are removed. This latter problem, i.e., the fact that 80% of the cancers in this category were from females in one plant with 1.5 years or less of exposure, is illustrated by the Nicholson et al. (1987) study which found no such associations in persons with much greater exposure and latency periods. Brown states, *"The update provides limited information ... . The limitations of this study include: (1) possible misclassification of the cause of death, ... it is not clear in every case that the cause of death was due to primary cancer of the liver, gall bladder, and biliary tract; (2) the category of death found in excess includes cancer types that are different from those found in animals exposed to PCBs; and (3) the pattern of risk by latency and duration of employment is not completely consistent with that of an occupational carcinogen, ..."* Given the above limitations, it can only be concluded that no association emerges from these studies, and each purported association is, at best, tenuous.

Temporal and dose-reponse relationships are clearly not evident in the present epidemiological studies. Bertazzi et al. (1987) concluded that, *"Analysis by duration of exposure, latency, and year of first exposure did not reveal any definite pattern or trend of mortality for any of the relevant causes."* Brown (1987) similarly found no clear association between length of employment (as a measure of exposure) and cancer, nor was latency observed. In fact, in both of these cohorts the cancers of most concern were observed in individuals with lesser exposure. This is inconsistent with the dose-response relationship for all chemically-induced cancer. Dose-response and latency relationships were also not developed in the cohort studies of Gustavsson et al. (1986) and Nicholson et al. (1987).

With respect to biological plausibility, observations in animals suggest that it is possible for PCBs to produce hepatocellular cancer. Other forms of cancer

do not appear to be elevated and may in fact be reduced by PCB exposure. As noted by Brown (1987), the categories of death reported to be in excess in each human epidemiologic study is different from that found in animals exposed to PCB viz hepatocellular carcinoma. Because of this inconsistency there is only limited evidence for biological plausibility.

With respect to the criterion of coherence, this condition clearly has not been met. There has been an inconsistency in the reporting of types of cancers elevated between studies and between the types of cancers found elevated in each sex within specific studies. None of the temporal or dose relationships expected for chemical carcinogenicity have been observed in any study.

In conclusion, these six criteria provide a useful framework with which to evaluate the evidence for human carcinogenicity of PCBs provided by mortality studies of occupationally-exposed workers. While it might not be reasonable to expect that each of the six criteria be fulfilled before an association is made between an exposure circumstance and a disease (in this case cancer), it is, however, reasonable to expect that most of the criteria are fulfilled before an association is accepted. In the case of PCB exposure and any other specific type of cancer, or cancer in general, only one criteria can be considered met (biological plausibility). And this criterion has only been met to a limited degree. Current evidence, therefore, does not indicate an association between PCB exposure and cancer in humans.

Appendix A

The Yusho and Yu-Cheng Poisonings

1.0 THE YUSHO AND YU-CHENG POISONINGS

Massive, non-occupational human exposure to PCBs in cooking oil occurred in Japan and Taiwan in 1968 and 1978, respectively. In total, the number of persons affected by these incidents has reached nearly 4,000 persons. The Japanese (termed "Yusho") and Chinese (termed "Yu-Cheng") incidents are markedly similar with respect to their symptomatology and likely causal agents. Although the PCB mixtures Kanechlor 400 and Kanechlor 500 have been blamed for causing the toxic symptoms associated with exposure to the contaminated rice oil, it now appears that low levels of polychlorinated dibenzofurans (PCDFs) present in the rice oil were primarily responsible for the adverse health effects observed in both toxic exposures (Kunita et al., 1984; Hori et al., 1982; Bandiera et al., 1984; Kashimoto and Miyata, 1986). Thus, in light of the concomitant exposure of humans to PCDFs, it is difficult or impossible to draw any conclusions regarding the toxicity of PCBs from the Yusho and Yu-Cheng experiences.

1.1 The Yusho Incident (Japan)

"Yusho," which translated means "oil disease" or "rice oil disease," is the term used to describe the symptoms experienced by 1,788 Japanese after they used cooking oil which was contaminated with PCB (Kanechlor 400) during processing. Early studies appeared to implicate PCB as the sole agent responsible for the symptoms of Yusho (Kuratsune et al., 1969; 1972), but later analyses of the contaminated oil also detected the presence of polychlorinated dibenzofurans (PCDFs) and polychlorinated quaterphenyls (PCQs) (Nagayama et al., 1976; Kamps et al., 1978). It was estimated that the total ingestion of PCBs, PCDFs, and PCQs by the average Yusho victim was 633, 3.3, and 596 mg, respectively (Hayabuchi et al., 1979).

Since the outbreak of Yusho in 1968, many epidemiological studies have examined the clinical signs and symptoms particular to this toxic exposure. The most notable initial signs were darkening of the nails, acne, skin pigmentation, increased eye discharge, swelling of the eyelids, acne, and hyperemia of the mucous membranes of the eyes. Subjective complaints such as

weakness, itching, headache, and numbness were also reported. Kuratsune et al. (1972) reported no incidence of these signs and symptoms in a control Japanese population.

Systemic intoxication in Yusho victims is reported to involve the nervous system, liver, lipid metabolism, skin, and eyes. Initially, dermatologic problems in persons exposed to the contaminated oil were among the most important symptoms used to diagnose Yusho victims (Urabe and Asahi, 1984). As presented in Table 1.1, a majority of 189 Yusho patients examined had acne and skin eruptions, blackening of the nails, skin color changes, and black spots in the pores. Acneform eruptions developed primarily on the face, auricles, retroauricular areas, inguinal areas, and external genitalia. Pigmentation of the skin occurred mainly on the nails of the toes and fingers, gingivae, face, palpebral conjunctivae, and lip. Cysts and closed comedones were reported to be significantly decreased three to four years after the initial diagnosis. Black comedones were found to disappear five or six years after diagnosis. Follicular cysts disappeared within 4-10 years, with cysts persisting longer in more severely affected individuals (Urabe and Asahi, 1984). The most prominent ocular signs of intoxication in Yusho victims were hypersecretion of the meibomian glands, pigmentation of the conjunctiva, and swelling of the upper eyelids (Urabe and Koda, 1976; Kohno et al., 1985).

Symptoms in Yusho victims also suggest the possibility of Yusho-induced neurological effects. Nerve conduction velocity measurements of 23 Yusho victims indicated slowing of the sural and/or radial nerve conduction velocity in nine victims. Two victims demonstrated evidence of slowed motor nerve conduction velocity (Kuroiwa et al., 1969). From results of the above study, Okumura (1984a&b) indicated that peripheral neuropathy which primarily involves the sensory nerves may be among the effects experienced by Yusho victims. Yoshimura and Hayabuchi (1985) questioned housewives of families in which Yusho occurred, and found a significant correlation between estimated ingestion of contaminated rice oil and symptoms relating to the peripheral nervous system (i.e., numbness of limbs). Although headache was a major complaint among those exposed to the contaminated oil, no study has detected any adverse central nervous system effect in Yusho patients. Okumura

Table 1.1

Signs and Symptoms of Adult Male and Female Japanese Examined After the Onset of Yusho

Percentage of patients reporting signs or symptoms	Males (n = 89)	Females (n = 100)
Signs		
Increased eye discharge	88.8	83.0
Acne-like skin eruption	87.6	82.0
Blackening of nails	83.1	75.0
Skin color changes	75.3	72.0
Swelling of upper eyelids	71.9	74.0
Hyperemia of mucous membranes of eyes	70.8	71.0
Black spots in all pores	64.0	56.0
Pigmentation of mucous membranes	56.2	47.0
Temporary visual problems	56.2	55.0
Excessive sweating in palms	50.6	55.0
Hardening of backs of hands	24.7	29.0
Vomiting	23.6	28.0
Red spots on limbs	20.2	16.0
Swelling of hands and feet	20.2	41.0
Fever	16.9	19.0
Diarrhea	19.1	17.0
Jaundice	11.2	11.0
Symptoms		
Sense of weakness	58.4	52.0
Itching	42.7	52.0
Numbness of hands and feet	32.6	39.0
Headaches	30.3	39.0
Hearing difficulty	18.0	19.0
Spasms of hands and feet	7.9	8.0

Adapted from Kuratsune et al. (1972)

(1984a&b) failed to demonstrate any relationship between blood PCB level and headache complaints in Yusho victims. Nagamatsu and Kuroiwa (1979) also found no evidence of electroencephalographic (EEG) abnormalities in 20 Yusho victims.

Apart from proliferation of the hepatic smooth endoplasmic reticulum (Hirayama et al., 1969) and slight hepatomegaly (Hirayama, 1976), few liver changes have been detected in Yusho victims. No consistent abnormality was encountered in liver function tests including the bromosulphalein test (Okumura, 1984a&b), and no signs of hepatotoxicity were found among Yusho victims at autopsy (Kikuchi, 1984).

Clinical laboratory examinations of Yusho victims suggest that metabolic changes may be associated with exposure to the contaminated rice oil. Okumura et al. (1979) studied serum triglyceride levels in nine male and 15 female patients over a 10-year period from 1969-1978. Triglyceride levels in men were too variable to draw any conclusion regarding a tendency toward decreasing serum triglyceride levels with time. However, a trend toward declining triglyceride levels in women was discernible. The highest triglyceride levels detected in women in 1970 and 1971 were significantly higher ($0.1 > p > 0.05$) than the average level in the last year of the study (1977-1978). Ingestion of contaminated rice oil did not appear to be associated with high blood pressure (Akagi and Okumura, 1985). Hypobilirubinemia was also detected in Yusho victims, but the clinical significance of this finding is unknown (Hirayama et al., 1974).

Nakanishi et al. (1985a&b) have reported that serum immunoglobulins, viz. IgA and IgM, were decreased in Yusho patients in early stages of the disease, but later returned to normal levels. The ratio of T4 (T helper cells) to T8 (T suppressor cells was increased and responsiveness of lymphocytes to phytohemagglutinin (PHA) was diminished, though these changes were of doubtful statistical significance. Interestingly, patients poisoned with contaminated rice oil in Taiwan showed the opposite response, i.e. the T4/T8 ratio was decreased and responsiveness to PHA was enhanced.

Other effects described in detail which may be related to the Yusho incident

include endocrine disorders, growth retardation, and fetotoxicity. Although no set pattern of symptoms suggestive of endocrine abnormalities was observed, a majority of female Yusho patients (60%) had a high incidence of menstrual difficulties such as prolongation, shortening, or irregularity of the menstrual cycle. The duration of menstrual flow was also variable in 55% of female Yusho patients. Urinary output of estrogens in female Yusho victims determined one to two years after the incident tended to be lower than the normal range. The reasons for these symptoms and clinical laboratory findings are unclear, but primary ovarian disorders and increased metabolism of sex hormones by the liver have been suggested as possible explanations for the observed menstrual irregularities in Yusho victims (Hirayama, 1976). No endocrine problems in male Yusho victims have been reported.

Growth retardation in young Yusho victims was reported for a group of 23 boys and 19 girls in the year following the incident. These children were compared with matched controls for height and body weight gain in the year preceding the Yusho incident and the year following the exposure. When compared with controls, height and body weight gain were significantly decreased in exposed boys one year after poisoning. Some recovery of the growth rate in the affected children was observed two to three years after the exposure (Hirayama, 1976).

Children born to mothers affected by Yusho were observed to have abnormal pigmentation of the skin and gingiva, increased eye discharge, and were smaller than national standards. Infants born to Yusho mothers also had eruption of teeth at birth, larger frontal and occipital fontanelles, and wider than usual sagittal suture (Kuratsune et al., 1969; Kuratsune, 1976a; Rogan, 1982; Yamashita and Hayashi, 1985). A relationship between maternal exposure to contaminated oil and severity of fetal effects has been difficult to demonstrate, however. Pigmented skin in affected infants faded two to five months after birth.

1.2 The Yu-Cheng Incident (Taiwan)

In many respects, the Yu-Cheng incident is very similar to the Yusho

incident which occurred in Japan. In both incidents, rice oil contaminated with Kanechlor was consumed. The Taiwanese incident, which occurred in Taichung county in May, 1979, involved both Kanechlor 400 and 500 and eventually affected 2,062 people. Affected persons developed many of the symptoms observed in Yusho victims such as follicular accentuation, pigmentation of the skin and nails, and hypersecretion of the meibomian glands (Lee et al., 1980; Wong et al., 1982; Fu, 1983; Lu and Wong, 1984). It is also known that like Yusho victims, Yu-Cheng victims were also exposed to PCDFs and PCQs in addition to PCB. The total average intake of PCBs, PCDFs, and PCQs by Yu-Cheng victims during the incident was estimated to be 973, 3.8, and 586 mg, respectively (Chen et al., 1981, 1984, 1985a). These intakes are similar to those estimated for Yusho victims.

Based on dermatological and ocular signs, Hsu et al. (1984;1985) graded the severity of the clinical symptoms of 1,670 Taiwanese exposed to the contaminated rice oil. These criteria and the results of the classification of exposed persons are presented in Table 1.2. Symptoms were not present or comparatively mild in 50% of the study population (grades 0 and 1) and more severe in the remainder of the persons examined (grades 2-4). Other symptoms, signs, and complaints of Yu-Cheng victims are listed in Table 1.3. Although the incidence of symptoms and signs of victims of Yu-Cheng poisoning do not exactly match those presented for Yusho patients in Table 1.1, the types of signs and symptoms are very similar.

In addition to the general signs and symptoms of Yu-Cheng disease, Lu and Wong (1984) identified possible Yu-Cheng-induced hepatic, neurological, immunological, and metabolic changes based upon their case studies (see symptoms and clinical findings presented in (Tables 1.3 and 1.4). Liver function tests in 276 patients revealed that serum transaminase (SGOT and SGPT) and bilirubin levels were significantly greater than controls but that LDH values were normal (Table 1.3).

Table 1.2

Classification of 1,670 Taiwanese Persons Exposed to Contaminated Rice Oil into Five Grades Based on Severity of Dermatological and Ocular Symptoms

Grade	Distribution	Diagnostic criteria
0	9%	*"Abnormal" blood levels of PCBs but no clinical symptoms
1	41%	Cheese-like discharge from the Meibomian gland; pigmentation of the nails
2	26%	Grade 1 plus comedones
3	14%	Grade 2 plus acneform eruption and limited sites of follicular opening
4	6%	Grade 3 with extensive acneform eruptions and widespread follicular opening

*For this study, "abnormal" PCB blood levels were defined as being ≥ 3 ppb. Table adapted from Hsu et al. (1984)

Table 1.3

Liver Function Tests in 143 Yu-Cheng Patients

Group	SGOT (K.U.)	SGPT (K.U.)	Bilirubin (mg%) Direct	Bilirubin (mg%) Total	LDH (U/L)
Patient (range)	43.2±28.1[a] (10.0-209.0)	44.8±31.6[a] (4.0-246.0)	0.29±0.13[a] (0.08-0.66)	0.56±0.14[a] (0.30-1.02)	92.4±27 (42-148)
Control (range)	22± 7[a] (5-40)	16±9[a] (5-35)	0.11±0.05[a] (0.1-0.4)	0.62±0.25[a] (0.3-1.1)	--- (52-149)

[a] $p<0.05$

Adapted from Lu and Wong (1984)

Table 1.4

Symptoms, Signs, and Complaints of 358 Taiwanese Persons Examined After the Onset of Yu-Cheng

	Percentage of patients reporting signs, symptoms, or complaints
Symptoms and signs	
Increased discharge from the eyes	29.1
Swelling of the eyelids	18.4
Acne-comedones	9.7
Disturbance in vision	9.5
Soreness or weakness of the limbs	7.3
Pruritis	5.6
General malaise	4.7
Soreness or irritation of the eyes	4.5
Numbness of the limbs	3.4
Headache, dizziness	3.4
Swelling or pain of the joints, foot	2.5
Pigmentation of the nails	2.5
Reduced appetite	0.8
Complaints	
Disturbance of vision, easily fatigued	51.4
Malaise	37.3
Numbness of the limbs	37.3
Pruritus	35.6
Headache, dizziness	21.9
Soreness, irritation of the eyes	18.8
Neck pain, lumbago	15.6
Cough	14.2
Abnormal menstruation	10.7*
Soreness, pain, or swelling of limbs, joints	6.8
Reduced appetite	4.9

*Note: 10.7% of female patients.
Adapted from Lu and Wong (1984)

Neurological studies of Yu-Cheng patients indicate the development of peripheral neuropathy in some affected persons (Lu and Wong, 1984; Chia and Chu, 1984;1985; Chen et al., 1985b). For example, Chia and Chu (1985) tested motor and sensory nerve conduction velocities (NCV) and amplitudes in 28 Yu-Cheng patients and 44 control subjects and compared test results in 1980 with those obtained in 1982. Mean motor nerve conduction velocities (ulnar and tibial) and sensory nerve velocities (radial and sural) in Yu-Cheng patients were significantly slower than controls ($p < 0.001$ to $p < 0.1$) in 1980 and 1982. Mean nerve amplitudes were significantly lower ($p < 0.001$ to $p < 0.1$) in Yu-Cheng patients in 1980 and 1982 when compared to controls. Although test results in 1982 appeared to be improved over 1980 results, the differences were not statistically significant. The incidence of neurological signs and symptoms in 1982 was not significantly different from 1980. Average PCB blood levels in Yu-Cheng victims declined to 19.2 ppb in 1982 from 35.9 ppb in 1980, but no correlation between mean blood PCB levels and the incidence of neurological signs and symptoms was found.

In a larger study, Chen et al. (1985b) measured motor and sensory nerve conduction velocities in 110 Yu-Cheng victims in an attempt to correlate neurological abnormalities with PCB, PCQ, and PCDF blood levels. In the study group, 43.6% and 21.8% of patients had slowed sensory nerve and motor nerve conduction velocities, respectively. Although the authors were able to demonstrate that Yu-Cheng patients had significantly slower nerve conduction velocities than historical controls, no statistically significant correlation between blood levels of PCBs, PCQs, or PCDFs and nerve conduction velocities could be determined. There was also no difference in PCB, PCQ, and PCDF blood levels in persons complaining of headaches and those without headaches. Patients with PCQ blood levels below 6.6 ppb were found to have significantly faster median nerve conduction velocities than persons with PCQ blood levels greater than 9.0 ppb. Similarly, persons with PCB levels below 24.0 ppb had significantly faster peroneal nerve conduction velocities than groups with PCB blood levels from 37.5-52.2 ppb and above 52.2 ppb.

Yu-Cheng patients have also been found to exhibit immunological changes such as decreased serum IgA and IgM concentrations, decreased percentages of total T cells, active T cell, and T helper cells (Chang et al., 1981; Lu and Wu, 1985), decreased delayed-type hypersensitivity response (Chang et al., 1982; Wu et al., 1984a; Lu and Wu, 1985), and enhanced lymphocyte response to mitogens *in vitro* (Lu and Wong, 1984; Wu et al., 1984a; Lu and Wu, 1985). Chang et al. (1981) examined blood samples from 30 Yu-Cheng patients and 23 normal subjects and detected lower mean percentages of active T cells (11.3% versus 22.1% for controls) and total T cells (41.7% versus 63.3% for controls) in Yu-Cheng patients. B cells were not affected. Mean serum immunoglobulin A and M levels in patients were 75% and 61% of controls, respectively. Percentages of active T cells were negatively correlated with blood PCB concentrations. The authors suggested that the immunological changes in Yu-Cheng patients were due to PCB exposure but failed to consider the involvement of PCQs and PCDFs in causing immunological changes. Even though blood or adipose levels of PCQs and PCDFs were not determined in this study, it may be assumed that persons with high PCB blood levels also had high PCQ and PCDF levels. Thus, it cannot be assumed that the effects observed are attributable to PCBs alone.

Chang et al. (1982) also evaluated delayed-type hypersensitivity responses of 30 Yu-Cheng victims to subcutaneous injections of streptokinase and streptodornase. PCB blood levels in patients ranged from 15.5 to 98.4 ppb. Thirteen Yu-Cheng patients had a positive reaction to the streptokinase-streptodornase injections while 40 of 50 control subjects had a positive response. A statistically significant positive correlation (correlation coefficient, 0.74) was observed between the severity of dermatological signs and PCB blood concentration in Yu-Cheng victims. The size of the induration produced by the streptokinase-streptodornase injection correlated negatively with PCB blood concentration (correlation coefficient, -0.54).

Evaluation of delayed-type skin responses is associated with some subjective interpretation. In this study, Chang and coworkers apparently failed to account for investigator bias by not using double blinded skin test readers. Also, it was

not known whether more than one reader was used or whether the skin reading process was consistent among multiple readers. As in their previous study of Yu-Cheng patients (Chang et al., 1981), Chang and coworkers attributed the observed immunological effects in this study to PCB exposure but failed to consider PCQs and PCDFs as possible causes of these effects.

Lu and Wong (1984) examined the *in vitro* responses of lymphocytes obtained from 83 Yu-Cheng patients (treatment lymphocytes). Lymphocytes were stimulated with various mitogens and the response compared with results from 35 healthy controls (control lymphocytes). The mean response of treatment lymphocytes to phytohemagglutinin was 30% greater than control. However, there were no significant differences between the responses of treatment lymphocytes and control lymphocytes to concanavalin A or pokeweed mitogen. Treatment lymphocytes proliferated to a greater extent than controls when stimulated with a purified protein derivative of tuberculin. This difference was apparent only after seven days of lymphocyte culture. No difference was observable after five days of culture.

In a similar report, Wu and coworkers examined immune function in 83 Yu-Cheng patients and compared them with 38 age- and sex-matched controls (Wu et al., 1984a). This study was conducted one year after the poisoning, and blood PCB concentrations in the Yu-Cheng group ranged from 4 to 558 ppb; the mean level was 149.5 ppb. Yu-Cheng patients had a lesser incidence of delayed hypersensitivity reaction to tuberculin and a generally enhanced proliferative response of lymphocytes to mitogens (phytohemagglutinin and pokeweed mitogen but not conconavalin A). No difference was found between the Yu-Cheng patients and controls with respect to leukocyte migration inhibition. The altered hypersensitivity response and response to mitogens were not correlated with PCB levels in the Yu-Cheng group.

In an apparent follow-up study, 30 Yu-Cheng patients were examined three years after exposure and compared with 38 unexposed control subjects (Wu et al., 1984b). No difference in delayed hypersensitivity to tuberculin was observed. Responsiveness of lymphocytes to mitogens was also similar in exposed and unexposed groups, except the Yu-Cheng patients had higher spontaneous rates

of proliferation. When lymphocyte populations were examined, Yu-Cheng patients had normal total lymphocyte counts and peripheral T- and B- cell numbers. The T4/T8 ratio was altered in the Yu-Cheng group (T4 cells were decreased while T8 cells were increased), though this change was not correlated with PCB level. Results of the original study and follow-up were also presented in a subsequent report (Lu and Wu, 1985).

The mean blood triglyceride level in 143 Yu-Cheng patients (200.9 mg%) was 63% higher than that of controls (123 mg%) (Lu and Wong, 1984). This observation is consistent with the elevated blood triglyceride levels seen in Yusho patients.

Wong et al. (1985) investigated the level of placental mixed function oxidase (MFO) three years after the Yu-Cheng incident in four women exposed to the contaminated rice oil. These women had PCB plasma levels ranging from 18-72 ppb and exhibited signs and symptoms typical of Yu-Cheng victims such as pigmented skin and acne. Babies born to the mothers in the study had somewhat lower birth weights than the normal average and one infant was born with pigmented skin. Aryl hydrocarbon hydroxylase activity levels in the placentas from these women ranged from 66-438 pmol benzo[a]pyrene formed/mg protein/hour. The control level in unexposed Taiwanese mothers was 0.3. It is clear that contaminated rice oil induced placental MFO in these mothers. However, the potential health effects due to placental enzyme induction, if there are any, are unknown.

In a small clinical study, Sunahara et al. (1987) recently examined age-matched Taiwanese mothers with and without Yu-Cheng disease. Among eight maternal pairs, the birth weights of children were compared and maternal blood and placental samples were taken for analysis of PCB and PCDF congeners, Epidermal Growth Factor (EGF) autophosphorylation capacity and kinetic characteristics, and placental benzo[a]pyrene hydroxylase activity. Mothers with Yu-Cheng disease gave birth to children with significantly lower birth weights than controls (2.86 vs. 3.37 kg) and exhibited a significantly decreased (> 50%) placental EGF autophosphorylation capacity. EGF receptor affinities were apparently not altered by Yu-Cheng disease. Placental

benzo[a]pyrene hydroxylase activity was significantly higher; two PCDF congeners (2,3,4,7,8- and 1,2,3,4,7,8-chlorodibenzofurans) and five PCB congeners (mainly 2,2',4,4',5,5'- and 2,2',3,3',4,4',5-chlorobiphenyl) were detected in the blood and placenta of most Yu-Cheng mothers. Significant correlations ($p < 0.05$) were observed between lowered birth weight and placental 1,2,3,4,7,8-chlorodibenzofuran content. EGF receptor autophosphorylation capacity correlated significantly with total placental PCBs and placental levels of 2,2',4,4',5,5'- or 2,3,3',4,4',5-chlorobiphenyl. Based upon the correlation between total placental PCBs and EGF receptor autophosphorylation capacity ($p < 0.01$), Sunahara et al. (1987) concluded that PCBs in contaminated rice oil may be responsible for diminished autophosphorylation of the EGF receptor. They further suggested that changes in placental EGF functions may serve as a useful marker for lowered birth weight in individuals exposed to PCBs or PCDFs, although it is unclear why this sophisticated and time-consuming assay would be considered a more desirable index of diminished birth weight than the birth weight itself.

The results of the Sunahara et al. study must be interpreted with caution. Although EGF-stimulated receptor autophosphorylation was correlated with lower birth weight, the physiological function of EGF-stimulated autophosphorylation in the placenta is unknown. There is nothing to indicate that it is necessarily related to birth weight on a cause-and-effect basis, and the correlation may have arisen simply because both effects occurred in the same study group, i.e. the Yu-Cheng women. Further, while PCB levels were best correlated with alterations in EGF-stimulated autophosphorylation, they were not significantly correlated with birth weight changes ($p=0.08$). The only halogenated aromatic hydrocarbon measured which correlated significantly with decreased birth weight was 1,2,3,4,7,8-hexachlorodibenzofuran. Therefore if any conclusion is supported by these data with respect to cause of the diminished birth weights in the children of Yu-Cheng women, it is that this effect is associated primarily with PCDF exposure.

Rogan et al. (1988) recently evaluated the health and development of children born to women with Yu-Cheng disease. The study involved 74 women with a history of Yu-Cheng who had living children born between June 1978 and

March 1985. The control group were children from 96 unexposed women who lived in the same neighborhoods. The frequency of some abnormalities at birth were higher in the exposed group of infants. Exposed mothers reported lower birth weights (mean ± SE: exposed, 2749 ± 46 grams, n = 128; controls, 3228 ± 40 grams, n = 115). Hyperpigmentation, conjunctivitis, nail changes, natal teeth, and bronchitis were more frequent in exposed infants than in controls, as reported by the mothers. Upon physical examination in 1985, exposed children were smaller than controls, but the difference between the groups was not significant. Exposed children had more gum hypertrophy, hyperpigmentation, and nail deformities than controls, but acne and conjunctival cysts were not more prevalent. Some conditions (e.g., hyperpigmentation and nail deformities) were found in higher frequency in 1985 than at birth in both control and exposed children, which complicates interpretation of the findings.

There were no abnormal reflexes or other localized neurological findings in exposed children, but the examining neurologists had an overall impression of developmental or psychomotor delay in twelve (10%) of the exposed children compared with three (3%) of control children, and of a speech problem in eight (7%) exposed and three (3%) unexposed children. On the behavior assessment tests, exposed children performed more poorly on the Bayley Scales for Infant Development (used until age 30 months), the Stanford-Binet IQ test (used from age 30-72 months), and the Rutter scale. Exposed children did not differ from controls in the verbal IQ score on the Wechsler Intelligence Scale for Children (WISC; used after age 72 months), but had lower average scores for performance IQ and full IQ. Statistical comparisons of these test scores were not reported. However, differences in average test scores between exposed and control children were relatively small compared to the variability within groups, and it is doubtful that any of these differences would be of statistical significance.

Most of the effects found in higher frequency in the exposed children were mucocutaneous symptoms that were commonly present in adult Yu-Cheng patients. These effects in adults have been attributed to PCDF contaminants rather than to PCBs. The role of PCDFs is further supported by a study of children whose parents were exposed to PCBs occupationally (Hara, 1985). In this population, PCDF exposure was substantially less than that for the

Yu-Cheng population, yet maternal blood PCB levels were comparable (Rogan et al., 1988). In contast to the reported findings in Yu-Cheng children, the children of occupationally-exposed parents were not small for their gestational age and PCB levels were not associated with a greater frequency of mucocutaneous symptoms. Thus, the effects observed in the Yu-Cheng children were most probably related to PCDF exposure and not PCB exposure.

1.3 Relevance of the Yusho and Yu-Cheng Incidents to PCB Poisonings

Although the relative contribution of PCB, PCQ, and PCDF to the toxic effects of Yusho and Yu-Cheng is difficult to determine, recent evidence suggests that PCDF may have been the most important toxic agent in rice oil poisoning (Masuda and Kuratsune, 1979; Kunita et al., 1984; Hori et al., 1982; Bandiera et al., 1984; Kashimoto and Miyata, 1986). It is reasonable to suggest that while these classes of polychlorinated organic compounds may have similar toxic effects, the potencies of PCQs and PCBs are much lower than that observed for PCDFs. In studies using cynomolgus monkeys, feeding PCB or PCQ alone at a dose of 5 mg/animal/day produced no dermal lesions which were characteristic of Yusho or Yu-Cheng victims. However, monkeys fed a mixture of 4.98 mg PCB + 0.02 mg PCQ + 0.002 mg PCDF/animal/day suffered hair loss, edema of the upper eyelids, skin pigmentation, acneform eruptions on the face, and dermal hyperkeratosis. The same dermal lesions as those produced by the PCB-PCQ-PCDF mixture were observed in monkeys fed only 0.020 mg of PCDF per day. In a separate experiment, rats fed a mixture of 1 mg PCB, 1 mg PCQ, and 0.01 mg PCDF daily for 21 days had decreased body weight gain, liver hypertrophy, and thymic atrophy. The ratio of these three compounds is similar to their ratio in Yusho oil. Rats fed 1 mg PCQ per day for this same period developed no observable effects. The only effect induced by feeding 1 mg PCB per day was liver hypertrophy. Rats fed 0.01 mg PCDF per day were affected in a similar manner and degree of severity as rats fed the PCB-PCQ-PCDF mixture (Kunita et al., 1984). Similarly, Hori et al. (1986) found that either a mixture of PCBs, PCDFs, and PCQs resembling the composition of toxic rice oil, or PCDFs alone, produced toxic symptoms in rats (suppression of body weight gain, immunosuppression, and altered serum biochemical findings) while PCBs or

PCQs alone did not.

Additional support for PCDFs as etiologic agents in Yusho and Yu-Cheng comes from studies such those by Bandiera and coworkers (1984) and Masuda and Yoshimura (1984). These investigators compared the relative effects of single doses of PCBs and PCDFs on rats by examining hepatic microsomal enzyme activities and organ weights. Bandiera and coworkers prepared similar mixtures of PCB and PCDF compounds to those present in the livers of Yusho patients. PCB compounds and their percentage by weight in the test mixture were 2,3',4,4',5-penta- (5.7%), 2,2'4,4',5,5'-hexa- (22.6%), 2,3,3',4,4',5-hexa- (28.2%), (2,2',3,4,4',5'-hexa- (12.3%), 2,2',3,4,4',5,5'-hepta- (19.1%), 2,2',3,3',4,4',5,-hepta- (12.2%) chlorobiphenyl. PCDF compounds and their percentage by weight in the test mixture were 2,3,7,8-tetra- (7.4%), 1,2,4,7,8-penta- (6.1%), 1,2,3,7,8-penta- (19.0%), 2,3,4,7,8-penta- (29.4%), 1,2,3,4,7,8-hexachloro- (38.1%) dibenzofurans. Immature Wistar rats were injected with single doses of the mixtures and were killed 14 days later. Liver aryl hydrocarbon hydroxylase (AHH) and liver ethoxyresorufin O-deethylase (EROD) activities were determined and body and thymic weights were measured. The PCB dose level required to increase AHH and EROD activities 4 and 40 fold were 15 and 50.1 mg/kg, respectively. In contrast, comparable AHH and EROD induction was induced by PCDF doses of 0.022 and 0.063 mg/kg, respectively. The doses of PCB and PCDF required to produce a 20% body weight loss were 398 and 0.18 mg/kg, respectively. PCDF was 2,210 times more potent than PCB in reducing thymic weights by 50%. By these criteria, the PCDF mixture was 680 to 2,210 times more potent than the PCB mixture.

Masuda and Yoshimura (1984) examined the effects of single intraperitoneal injections of separate PCB and PCDF congeners in Wistar rats. The isomers used in this study had previously been identified in blood and liver samples from Yusho victims. The effects of PCB and PCDF isomers on hepatic microsomal enzymes benzphetamine demethylase and benzo[a]pyrene hydroxylase were determined five days after injection. Liver, spleen, and thymus weights relative to controls were also measured. The PCDF isomers were much more toxic than the PCB isomers. The mean weight of thymuses from PCDF-treated animals was 40% of control, whereas thymuses from

PCB-treated animals were only slightly reduced or no different from the control. One of the most toxic PCDF isomers of those tested, 2,3,4,7,8-pentachlorodibenzofuran, was detected in the livers of Yusho patients in concentrations from 0.1 to 6.9 ppb. Total PCDF in the livers of these patients ranged from 0.16 to 17.6 ppb (Masuda and Yoshimura, 1984).

Other arguments which support the role of PCDFs as causal agents in the Yusho and Yu-Cheng incidents were discussed by Kashimoto and Miyata (1986). The conclusions of Kashimoto and Miyata regarding the role of PCB, PCQ, and PCDF in the Yusho and Yu-Cheng incidents are summarized below.

- The authors compared the severity of symptoms of a group of Japanese workers and Yusho patients. Although blood PCB levels of a group of Japanese workers and Yu-Cheng patients were similar, only Yu-Cheng patients had severe clinical manifestations of disease. Unlike the workers, Yu-Cheng patients were heavily exposed to PCDF, suggesting that the clinical manifestations of Yusho could best be explained by exposure to PCDF.

- PCQ blood levels in workers exposed to used PCBs were also similar to Yu-Cheng patients. Thus, the comparatively severe symptoms experienced by the Yu-Cheng patients are not explained by differences in PCQ exposure.

- In Yusho patients, blood PCB levels declined to near background levels five years after exposure. For this reason, PCBs are unlikely to be the cause of chronic symptoms of poisoning experienced by Yusho patients. In contrast, toxic isomers of PCDF have been shown to persist in the tissues of Yusho victims up to 10 years after exposure (Kashimoto et al., 1981).

Therefore, although Yusho and Yu-Cheng victims were exposed to an average of between 600 to 900 mg of PCB over the course of these incidents, the estimated exposure to 3.3 to 3.8 mg of PCDF appears to be responsible for many of the symptoms associated with these poisonings. As a class, PCDFs are much more toxic than PCBs, and it now appears that the large number of signs and symptoms experienced by Yusho and Yu-Cheng patients can be attributed to PCDFs.

1.4 Summary of the Yusho and Yu-Cheng Incidents

Yusho (Japan) and Yu-Cheng (Taiwan) have often been purported to represent two incidents of environmental exposure to PCBs. This mistake resulted, in part, from the fact that initial investigators of the health problems experienced by these victims were unaware of the large quantities of polychlorinated quaterphenyls (PCQ) and highly toxic polychlorinated dibenzofurans (PCDF) contained in the cooking oils responsible for these poisonings. Thus, while early authors viewed the Yusho and Yu-Cheng incidents as a PCB problem, more recent analytical and toxicological information has convincingly demonstrated that the toxic effects are due to the more toxic and persistent PCDFs. Therefore, the Yusho and Yu-Cheng incidents should not be viewed as examples of PCB poisoning but rather as evidence of the human health effects produced by the polychlorinated dibenzofurans.

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